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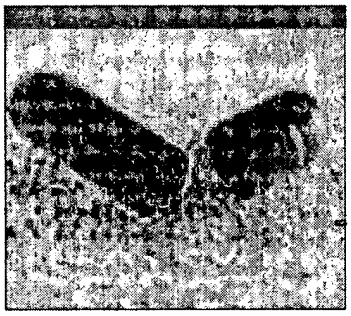

The Pain Market Outlook to 2011

By Melissa Zebrowski

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Prevalence of Cardiovascular Disease Risk Factors Among US Adults With Self-Reported Osteoarthritis: Data From the Third National Health and Nutrition Examination Survey

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Abstract

Objective: To estimate the prevalence of traditional risk factors for cardiovascular disease (CVD) among US adults with osteoarthritis (OA).

Methods: Using survey data from the Third National Health and Nutrition Examination Survey, we estimated the prevalence of selected CVD risk factors among a US OA and nonarthritic adult population. In additional analyses, we stratified the sample by gender and age (35-44, 45-64, and 65+ years) to further understand the CVD risk profile in an arthritic population and nonarthritic population. Relevant data on each survey participant's demographics, arthritis status, CVD risk factors, and sampling weights were obtained from the survey database.

Results: Of the 115.9 million US adults aged ≥35 years, 24.3 million (21%) have OA. Hypertension is prevalent in approximately 40% of OA patients; 20% of the patients smoke and 11% have diabetes. Prevalence of high total cholesterol is estimated to be 32%, while prevalence of low high-density lipoprotein cholesterol is estimated at 13%. Approximately 37% of OA patients are estimated to have renal impairment, but less than 1% suffer from renal failure.

Conclusion: National survey data suggest that, on average, US adults with OA have a high prevalence of cardiovascular risk factors. These findings highlight the need to consider patients' comorbidites when selecting the appropriate treatment options.

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Arthritis is a widely prevalent, disabling disease that places substantial demands on healthcare resources. It has been estimated that as many as 44 million outpatient visits and three quarters of a million hospitalizations annually are attributable to arthritis and its treatment, with associated direct medical care costs of $15 billion.[1,2] Estimates of lost productivity and other indirect costs of arthritis have been estimated to be as high as $50 billion annually.[1,2] The clinical and economic burdens of arthritis in the United States are expected to increase as the general population ages; an estimated 60 million Americans (nearly 20% of the population) are projected to have arthritis by 2020, of whom approximately one fifth (or 12 million people) will experience meaningful activity limitation.[1,3-5]

There is credible evidence that people with osteoarthritis (OA) and rheumatoid arthritis (RA) are at higher risk than the general population for several comorbid conditions, particularly cardiovascular disease (CVD).[6-8] Moreover, there is an established body of research suggesting that age-adjusted mortality risk is higher among RA patients relative to the general population.[7-17]

The etiology of the association between arthritis and CVD is not fully understood. Various theories about the relationship have been put forth in recent studies, most of which are based on the premise that patients with arthritis are at advanced risk for development of CVD by virtue of their unfavorable risk factor profile. However, there is inherent difficulty in sorting out the relevant causes of CVD

in arthritis patients as they differ from the general population in many aspects. Changes in body mass composition, changes in lipid profile associated with medication use (eg, glucocorticoids), and activity limitations resulting from chronic joint disease may all play a role in increased CVD risk.[18,19] Some investigators believe that vascular inflammation associated with increased levels of thiol compounds and C-reactive protein, as well as peroxidization of low-density lipoprotein, may play a significant role in CVD pathogenesis in patients with arthritis.[18,20] Medications taken for arthritis-related conditions have also been implicated for either directly or indirectly leading to atherosclerosis.[18,21,22] The most commonly implicated drugs are glucocorticoids (chiefly, prednisone), which can increase serum lipids and glucose levels and induce hypertension.[23] Methotrexate, another commonly prescribed arthritis medication, has been shown to increase serum homocysteine levels.[23,24]

Although national estimates of OA and RA prevalence have been reported,[1,3,4] to the best of our knowledge the prevalence of CVD risk factors among such people has not been estimated to date. To this end, the government-sponsored database on the health status of the US population—the Third National Health and Nutrition Examination Survey (NHANES III)—was used to develop national estimates of the prevalence of selected cardiovascular risk factors among adult patients with self-reported OA and a nonarthritic US adult population.

···MATERIALS AND METHODS···

Data Source

We estimated the prevalence of selected CVD risk factors among US adults aged ≥35 years by diagnosis, gender, and age category (35-44, 45-64, and 65+ years) using survey data from NHANES III.[25]

NHANES is one of the major programs in the series of health-related studies conducted by the National Center for Health Statistics, part of the US Centers for Disease Control and Prevention, over the past 35 years. NHANES is designed to assess the health and nutritional status of adults and children in the United States through interviews and direct physical examinations. The survey is unique in that it combines a home interview with physical examinations and a variety of diagnostic and laboratory tests conducted in a mobile examination center. NHANES III, which was conducted from 1988 to 1994, included approximately 40 000 people aged ≥2 months selected from households in 81 counties across the 50 US states. Using a complex, stratified, multistage probability cluster sampling design (with oversampling of young children, older people, blacks, and Mexican Americans), the survey yields nationally representative information on the health and nutritional status of the civilian, noninstitutionalized US population. Physical examinations and objective measures are employed when information cannot be furnished or is not available in a standardized manner through interviews or through records maintained by the health professionals who provide medical care to survey respondents.[25-27]

The 4 data files representing the major components of NHANES III are adult household, examination, laboratory, and dietary recall; more than 5000 data elements are collected. One section of the household adult questionnaire asks respondents to note whether a physician has told them that they have OA or RA, and when they were first told that they had the condition. Other sections of the questionnaire focus on diabetes, high blood pressure, CVD, musculoskeletal conditions, gallbladder disease, kidney conditions, respiratory and allergy conditions, vision and hearing, and dental care. Histories of smoking and chewing tobacco use are recorded on both the home adult questionnaire and examination questionnaire, while history of alcohol use is asked on the examination questionnaire. Other NHANES sections pertain to exercise, nutrition assessment, medicine/vitamin use, biochemistry values, and physical exam results. Biochemistry data collected con-

sist of hematologic tests, general biochemistry tests, urine tests, antibody tests, and diabetes testing profile. The physical exam consists of a physician's exam, dental examination, allergy skin test, audiometry, spirometry, bone densitometry, gallbladder ultrasonography, and fundus photography.[25,26]

CVD risk factors examined in this study, as derived from the Household Adult Questionnaire (HAQ) and Laboratory Data File components of the NHANES III database, include systolic blood pressure (SBP) and diastolic blood pressure (DBP), total and high-density lipoprotein (HDL) cholesterol, physician-diagnosed diabetes mellitus, renal impairment or failure based on serum creatinine levels, and current cigarette smoking. Arthritis status was derived from the arthritis section of the HAQ as described above. Smoking status was derived from the question, "Do you smoke cigarettes now?" Diabetes mellitus status was derived from questions asking respondents whether a doctor had ever told them that they have diabetes. All other risk factor data were obtained from the NHANES III Laboratory Data File. Hypertension as a CVD risk factor was defined as SBP >140 mm Hg or DBP >90 mm Hg, as defined by current National Institutes of Health *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VI) guidelines.[28] Renal impairment and failure were defined respectively as serum creatinine levels exceeding the upper limit and twice the upper limit of normal (ie, >1.5 mg/dL and >3 mg/dL, respectively), which reflects the methods of the Massachusetts General Hospital.[29]

Statistical Analyses

Prevalence (stated as percentages) and associated 95% confidence intervals (CIs) were estimated for each CVD risk factor among an OA and a nonarthritic population. Gender- and age-stratified prevalence rates were also estimated for each population. SUDAAN® statistical analysis software (Research Triangle Institute, Research Triangle Park, NC) in conjunction with Statistical Analysis System (SAS) Release 8.02 (SAS Institute, Cary, NC) were used for these analyses. SUDAAN is specifically designed for analysis of cluster-correlated data from surveys such as NHANES III that involve multistage sample designs. Robust variance estimates are generated that account for intracluster correlation, unequal weighting, stratification, and without-replacement sampling. To provide estimates that were representative of the US population, analyses of each data element incorporated sampling weights obtained from the NHANES III database. These weights account for the unequal probabilities of selection resulting from the cluster design, the planned oversampling of certain demographic subgroups, and nonresponse adjustment factors based on US Census Bureau data on age, gender, race, income, and geographic location of the US population.[26,27] Since our investigation focused on interval estimation rather than on hypothesis testing, no tests of statistical significance were undertaken.

···RESULTS···

Prevalence Estimates

Osteoarthritis. Of the 115.9 million US adults aged ≥35 years, 24.3 million (21%) have OA (95% CI, 22.1 million-26.6 million) (**Table 1**). Nearly two thirds of these people are women. Prevalence rates of OA increase with age in both genders. However, the ratio of females to males with OA increases with advancing age, from 1.32:1 among people aged 35 to 44 years to 1.88:1 among people aged ≥65 years.

Table 1 also shows that the nonarthritic population is considerably younger than the OA population. Over 47% of OA patients are older than 65 years, compared with only 19% of those in the nonarthritic population. In addition, there were gender differences between the arthritis and nonarthritic populations; nearly 63% of the OA population was comprised of women, compared with only 49.9% of the general nonarthritic population.

Table 1. Estimated Numbers of US Adults Aged ≥35 Years With Osteoarthritis, by Gender and Age

Gender and Age (Years)	Osteoarthritis Percentage of People (95% CI)		General Population Without Arthritis Percentage of People (95% CI)	
All (n)	24 345 370	(22 110 212-26 580 528)	85 800 548	(78 999 986-92 601 110)
35-44	13.30	(11.79-14.56)	41.41	(40.18-42.47)
45-64	39.49	(39.26-39.68)	39.59	(39.74-39.46)
65+	47.21	(45.01-49.04)	18.99	(17.85-19.97)
Men (n)	9 015 680	(7 874 587-10 156 773)	42 986 882	(39 689 389-46 284 375)
35-44	15.51	(12.70-17.69)	40.13	(38.36-41.65)
45-64	40.23	(38.75-41.38)	41.17	(41.02-41.30)
65+	44.26	(42.54-45.59)	18.70	(17.63-19.62)
Women (n)	15 329 690	(13 824 691-16 834 689)	42 813 666	(38 878 456-46 748 876)
35-44	12.00	(9.99-13.66)	42.70	(41.43-43.77)
45-64	39.05	(37.58-40.26)	38.01	(37.44-38.48)
65+	48.95	(46.67-50.82)	19.29	(17.81-20.52)

CI indicates confidence interval.

Hypertension. Approximately 40% (95% CI, 35.3-45.5) of people with OA have Stage I-III hypertension as defined by the JNC VI guidelines (Table 2).[28] By comparison, only about 25% (95% CI, 23.0-27.6) of the general population without arthritis was estimated to have hypertension. Prevalence of hypertension is slightly higher among men than women, and, as epidemiologic data suggest, higher among people aged ≥65 years versus younger people.

Cigarette Smoking. Approximately 20% (95% CI, 17.6-23.1) of OA patients are current cigarette smokers (Table 2). The crude rates in this analysis are slightly lower than that for the general population without arthritis, wherein about 26% (95% CI, 23.6-28.4) are smokers.

Diabetes Mellitus. Approximately 11% (95% CI, 9.2-12.9) of people with OA have diabetes mellitus (Table 2). By comparison, only about 6% (95% CI, 5.6-7.3) of the general population without arthritis is diabetic. When stratifying by gender, this analysis suggests that female OA patients were more likely to have diabetes mellitus than a nonarthritic population. Prevalence of diabetes is slightly higher among women than men, and, as epidemiologic data suggest, higher among older people.

Hypercholesterolemia. Approximately 32% (95% CI, 27.1-36.2) of people with OA have high total cholesterol levels (ie, ≥240 mg/dL) (Table 2). About 24% (95% CI, 21.4%-26.0%) of the general population without arthritis has high total cholesterol levels. Prevalence of high total cholesterol is slightly greater among women than men, and has a marked increase among people aged 45 years and older.

Low HDL Cholesterol. The prevalence of low HDL cholesterol (< 35 mg/dL) is similar, approximately 13% (95% CI, 10.8-16.1) in people with OA and 12% (95% CI, 10.4-13.2) in the general population without arthritis (Table 2). Prevalence of low HDL cholesterol is substantially higher among men than women, but there is little differentiation among the age categories.

Renal Impairment and Failure. Approximately 37% (95% CI, 31.6-41.5) of people with OA have renal impairment, manifested as serum creatinine levels exceeding the upper normal limit of 1.5 mg/dL (Table 2). Moreover, approximately 0.8% (95% CI, 0.4-1.3) of people with OA

have renal failure, defined as serum creatinine levels exceeding twice the upper normal limit (ie, ≥3.0 mg/dL). By comparison, it is estimated that only about 27% (95% CI, 23.8-30.3) of the general population without arthritis have renal impairment, and only 0.3% (95% CI, 0.2-0.4) have renal failure.

···DISCUSSION···

Patient-level examination data from the NHANES III have been used to estimate the prevalence of selected CVD risk factors among US adults with OA. Other studies assessing the prevalence of arthritis in the United States have been conducted, but the prevalence of traditional risk factors for CVD among arthritis patients has not been well quantified to date.

Estimates suggest that approximately 24.3 million US adults aged ≥35 years have OA, and that nearly two thirds of these people are women. These estimates are consistent with what has been reported elsewhere.[3]

Findings suggest that US adults with OA indeed may be at an increased risk of CVD relative to the nonarthritic population. For each of the risk factors examined, except cigarette smoking, point estimates of prevalence among OA patients exceeded those of the general population. While tests of statistical significance were not performed, it was observed that the difference in risk factor prevalence versus the general population is not statistically significant at the "conventional" $\alpha = 0.05$ level.

Our findings suggest that the prevalence of hypertension is significantly greater among OA patients versus patients without arthritis. Gabriel and colleagues[6] found the prevalence of diabetes to be 5.0% among 441 OA patients. The estimates from this study at 11% are considerably higher. This difference could be related to a different population sampling in the 2 studies.

Reports on total cholesterol levels among patients with arthritis are scant

Table 2. Estimated Prevalence of CVD Risk Factors Among US Adults Aged ≥35 Years With and Without Osteoarthritis

Cardiovascular Disease Risk Factors, Stratified by Gender and Age (Years)	Prevalence, % (95% CI)			
	Osteoarthritis (n = 24 345 370)		General Population Without Arthritis (n = 115 861 005)	
Hypertension (Stage I-III, JNC VI Guidelines*)				
All	40%	(35.3-45.5)	25%	(23.0-27.6)
35-44	14%	(7.5-19.7)	11%	(9.3-13.1)
45-64	32%	(26.4-37.3)	28%	(24.6-31.5)
65+	55%	(46.8-63.5)	50%	(42.9-57.8)
Men	41%	(33.4-47.7)	28%	(25.1-31.0)
35-44	20%	(6.8-33.1)	14%	(11.1-17.7)
45-64	33%	(22.1-43.5)	32%	(27.4-36.7)
65+	55%	(45.5-64.2)	49%	(41.2-56.0)
Women	40%	(34.9-45.7)	23%	(19.8-25.4)
35-44	9%	(2.8-14.8)	8%	(6.1-10.3)
45-64	31%	(25.1-37.3)	24%	(20.2-27.2)
65+	55%	(45.7-64.8)	52%	(41.8-62.6)
Cigarette Smoking				
All	20%	(17.6-23.1)	26%	(23.6-28.4)
35-44	25%	(16.1-34.5)	31%	(27.2-34.8)
45-64	31%	(26.1-35.9)	26%	(22.6-29.3)
65+	10%	(8.1-12.2)	15%	(12.3-17.8)
Men	25%	(19.5-29.9)	30%	(26.9-33.2)
35-44	34%	(13.5-54.2)	36%	(30.7-42.3)
45-64	35%	(24.6-44.7)	29%	(24.5-34.2)
65+	12%	(8.2-16.6)	18%	(13.4-22.1)
Women	18%	(15.2-20.5)	22%	(19.1-24.7)
35-44	19%	(11.1-26.4)	26%	(21.4-30.4)
45-64	29%	(23.0-34.5)	22%	(18.2-26.2)
65+	9%	(6.4-11.5)	12%	(9.9-14.8)
Diabetes Mellitus				
All	11%	(9.2-12.9)	6%	(5.6-7.3)
35-44	4%	(0.7-7.2)	4%	(2.3-5.1)
45-64	11%	(7.3-13.8)	7%	(5.8-8.3)
65+	13%	(11.0-15.9)	11%	(9.0-12.8)
Men	10%	(7.3-12.3)	7%	(5.4-7.7)
35-44	0%	(-0.2-1.1)	3%	(1.0-5.3)
45-64	9%	(4.2-13.5)	8%	(6.0-10.0)
65+	14%	(9.8-18.1)	11%	(8.8-13.2)
Women	12%	(9.5-14.1)	6%	(5.0-7.5)
35-44	7%	(1.0-12.4)	4%	(2.6-6.1)
45-64	12%	(7.6-15.7)	6%	(4.4-7.7)
65+	13%	(10.3-16.1)	11%	(7.9-13.8)
High Total Cholesterol (≥240 mg/dL)				
All	32%	(27.1-36.2)	24%	(21.4-26.0)
35-44	22%	(11.6-32.5)	15%	(12.9-17.5)
45-64	34%	(27.8-39.3)	29%	(26.0-31.9)
65+	33%	(26.3-39.3)	31%	(25.9-36.7)
Men	23%	(17.7-28.5)	23%	(20.2-25.6)
35-44	22%	(10.5-33.9)	19%	(15.7-22.5)
45-64	26%	(18.6-33.4)	27%	(23.4-31.0)
65+	21%	(13.9-27.6)	21%	(17.1-25.7)
Women	37%	(30.9-42.7)	24%	(21.8-27.1)
35-44	22%	(8.9-35.0)	12%	(9.2-13.9)
45-64	38%	(29.9-46.5)	31%	(27.2-34.5)
65+	39%	(31.4-47.3)	41%	(32.8-49.2)

(continued on next page)

*Systolic blood pressure >140 mm Hg; diastolic blood pressure >90 mm Hg (NIH Publication 98-4080, November 1997).

CVD indicates cardiovascular disease; JNC VI, *Sixth Report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure.*

Table 2. Estimated Prevalence of CVD Risk Factors Among US Adults Aged ≥35 Years With and Without Osteoarthritis *(Continued)*

Cardiovascular Disease Risk Factors, Stratified by Gender and Age (Years)	Osteoarthritis (n = 24 345 370)		General Population Without Arthritis (n = 115 861 005)	
Low HDL Cholesterol (<35 mg/dL)				
All	13%	(10.8-16.1)	12%	(10.4-13.2)
35-44	15%	(7.9-21.5)	11%	(9.2-13.8)
45-64	14%	(10.2-17.9)	12%	(10.0-13.5)
65+	13%	(9.9-15.2)	13%	(9.8-15.6)
Men	25%	(19.3-30.9)	18%	(15.9-20.8)
35-44	29%	(12.9-44.8)	18%	(13.7-22.3)
45-64	27%	(17.6-35.6)	19%	(15.6-21.7)
65+	22%	(15.9-29.0)	18%	(14.5-22.4)
Women	6%	(5.0-7.9)	5%	(4.0-6.6)
35-44	3%	(0.1-6.6)	5%	(3.4-7.5)
45-64	6%	(4.2-8.6)	4%	(2.9-5.3)
65+	7%	(5.1-9.2)	7%	(4.2-10.2)
Renal Impairment (Serum Creatinine Levels Above ULN, 1.5 mg/dL)				
All	37%	(31.6-41.5)	27%	(23.8-30.3)
35-44	18%	(11.1-25.0)	19%	(14.9-22.7)
45-64	28%	(22.3-33.2)	27%	(23.2-30.5)
65+	50%	(42.1-57.2)	46%	(39.1-53.5)
Men	38%	(31.3-44.1)	29%	(25.8-32.8)
35-44	24%	(9.0-38.3)	22%	(16.6-26.6)
45-64	26%	(18.0-35.0)	29%	(24.5-33.8)
65+	53%	(42.8-63.4)	47%	(39.2-54.5)
Women	36%	(30.3-41.5)	25%	(21.1-28.5)
35-44	14%	(8.0-19.1)	16%	(12.5-19.8)
45-64	28%	(21.6-35.3)	24%	(19.6-28.9)
65+	48%	(39.2-56.4)	46%	(37.0-54.4)
Renal Failure (Serum Creatinine Levels 2x ULN ≥3.0 mg/dL)				
All	0.8%	(0.4-1.3)	0.3%	(0.2-0.4)
35-44	0.0%	(0.0-0.0)	0.1%	(0.0-0.1)
45-64	0.2%	(0.0-0.5)	0.1%	(0.0-0.2)
65+	1.6%	(0.6-2.6)	1.0%	(0.5-1.4)
Men	1.0%	(0.2-1.8)	0.2%	(0.1-0.4)
35-44	0.0%	(0.0-0.0)	0.0%	(0.0-0.1)
45-64	0.3%	(-0.1-0.7)	0.2%	(0.0-0.3)
65+	2.0%	(0.1-3.9)	0.9%	(0.2-1.5)
Women	0.8%	(0.2-1.3)	0.3%	(0.1-0.4)
35-44	0.0%	(0.0-0.0)	0.1%	(0.1-0.1)
45-64	0.2%	(-0.1-0.5)	0.1%	(0.0-0.1)
65+	1.4%	(0.3-2.6)	1.0%	(0.2-1.9)

CVD indicates cardiovascular disease; HDL, high-density lipoprotein; ULN, upper limit of normal.

and somewhat contradictory. A prevalence rate of 32% was estimated in OA patients, which is higher than the 23% rate estimated for the general population. The comparatively lower prevalence of cardioprotective HDL cholesterol found in this study is consistent with what has been reported in other studies.[9,30-34]

Potential limitations of this study bear mention. First, it should be noted that due to the complex sampling design of NHANES III, extreme variability in the weights has the potential to result in reduced reliability of the estimates. However, the NHANES III sample was designed to minimize the variability in the weights through measures such as weight trimming. Although unlikely, extreme observations in conjunction with large weights may have resulted in extremely influential observations dominating the analyses.[27] Data from the NHANES surveys are considered by health services researchers to be among the most suitable-to-task for purposes of generating national estimates of disease incidence and prevalence. Nonetheless, because NHANES III is based on surveys of the civilian noninstitutionalized population, which represents 98% of the total US population, certain groups (eg, the institutionalized elderly) were excluded.[3] Although the NHANES sampling methodology accounts for factors such as this, estimates of disease and risk factor prevalence presented in this article could differ somewhat from true prevalence.

Identification of comorbid medical conditions in NHANES III is derived mainly from patient self-report rather than from physical examination. Moreover, the self-reported data are confirmed by physicians only in certain circumstances. The validity of using self-reports of arthritic conditions to estimate true prevalence of OA is unknown, but studies conducted in other disease areas suggest that self-reported measures selected from NHANES can be quite reliable. The sensitivity and specificity of self-reported hypertension in NHANES III has been assessed,[35] and the validity of using NHANES data in this fashion for surveillance of hypertension trends in the US population is well established. Also, self-reports of an arthritis diagnosis derived from NHANES data have been used to examine the association between arthritis incidence and use of estrogen replacement therapy, body mass index,

and weight change,[36,37] and to explore associations between arthritis diagnosis, educational attainment, and mortality.[38-40]

Because many people with arthritis may not consult a physician for their condition, they consequently may not be able to affirmatively answer the NHANES question regarding whether a doctor has told them they have arthritis. Furthermore, the possibility of faulty recall or other ascertainment bias among NHANES III participants cannot be ruled out. Patients whose health histories span many years may omit less serious health conditions, misplace dates of occurrence, or incorrectly remember the names of health conditions that were diagnosed several months or years in the past. Certainly, poor communication or a lack of understanding of medical terminology could be detrimental factors. Patients mistaking "rheumatism" for "rheumatoid arthritis" could be one example. A related concern is that the terms used to name or describe a given health condition vary among people of different language, cultural, social, or educational backgrounds. Compounding this problem is the fact that NHANES uses a checklist to collect information on chronic conditions and does not include definitions of the terms or lists of related symptoms to provide a consistent definition across subjects. However, NHANES has a deserved reputation for its clear, unambiguous diagnostic criteria and wording on its questionnaires. Although the self-reported information regarding arthritis in NHANES III has not been systematically validated, NHANES patient data has been used to ascertain prevalence of chronic disease, including arthritis, with wide acceptance since the 1970s. Self-reported rheumatoid arthritis was excluded from this analysis because it is unlikely that patients would be able to reliably report this diagnosis for all the reasons listed above.

Finally, one of the major limitations of this study was the relatively limited number of CVD risk factors that could be estimated using the NHANES III database. Interestingly, McEntegart and colleagues[9] and Wållberg-Jonsson and colleagues[18,41] in their studies of RA patients identified significant correlations between RA and several thrombotic predictors of CVD that we were not able to derive from NHANES III data, including fibrinogen, von Willebrand factor, plasminogen activator inhibitor 1, tissue plasminogen activator antigen, and fibrin D-dimer. Current thinking is that inflammatory factors that promote atherogenesis and thrombogenesis may play important roles in the development of CVD in arthritis patients, particularly those with RA. Had it been possible, estimation of prevalence rates for these potential risk factors would have been worthwhile.

···CONCLUSION···

National survey data suggests, on average, US adults with OA have a high prevalence of CVD risk factors, which is higher than that of a nonarthritic population. These differences are likely to be due to the different age and gender distributions between an arthritic and nonarthritic population. Prevalence estimates, such as the ones reported here, are not conclusive evidence that OA increases the likelihood of developing CVD risk factors or CVD. If anything, they provide further evidence that CVD and arthritis may represent separate end points of a similar pathological process.[42,43] While the importance of CVD risk factor reduction in all people is obvious, these prevalence estimates demonstrate that from a practical clinical perspective, modifiable CVD risk factors need to be aggressively managed in the arthritic population. It is important to be aware of the higher prevalence of CVD risk factors in the arthritic population when selecting from the many treatment options available today.

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Comparative Effectiveness Review
Number 4

Comparative Effectiveness and Safety of Analgesics for Osteoarthritis

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Background

Osteoarthritis is a chronic condition involving degeneration of cartilage within the joints. It is the most common form of arthritis and is associated with pain, substantial disability, and reduced quality of life. About 6 percent of U.S. adults aged 30 years or older have symptomatic osteoarthritis of the knee, and 3 percent have symptomatic osteoarthritis of the hip. Osteoarthritis increases with age: the incidence and prevalence increase two- to tenfold from age 30 to 65 and continue to increase after age 65. The total costs for arthritis, including osteoarthritis, may be greater than 2 percent of the gross domestic product, with more than half of these costs related to work loss.

Common oral medications for osteoarthritis include nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen. Patients with osteoarthritis also use over-the-counter supplements not regulated by the U.S. Food and Drug Administration (FDA) as pharmaceuticals, including glucosamine and chondroitin, as well as topical agents. Opioid medications are also used for selected patients with refractory, chronic pain but are not recommended for first-line treatment of osteoarthritis and therefore not included in this review. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may vary for individual drugs within a class. Nonpharmacologic interventions (such as physical therapy, weight reduction, and exercise) also help improve pain and functional status in patients with osteoarthritis.

A challenge in treating osteoarthritis is deciding which medications will provide the greatest symptom relief with the fewest serious adverse effects. NSAIDs decrease pain, inflammation, and fever by blocking cyclo-oxygenase (COX) enzymes. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-1 protects the lining of the stomach from acid. COX-2 is found in joint and muscle, and mediates effects on pain and inflammation. By blocking COX-2, NSAIDs reduce pain compared to placebo in patients with arthritis, low back pain, minor injuries, and soft tissue rheumatism. However, NSAIDs that also block the COX-1 enzyme (also called "nonselective NSAIDs") can cause gastrointestinal bleeding. In the United States, there are an estimated 16,500 annual deaths due to NSAID-induced gastrointestinal complications, a higher death rate than that for cervical cancer or malignant melanoma. Theoretically, NSAIDs that block only the COX-2 enzyme (also called "coxibs," "COX-2 selective NSAIDs," or "selective NSAIDs") should be safer with regard to gastrointestinal bleeding, but they also appear to be associated with increased rates of serious cardiovascular and other adverse effects. Less is known about COX-3, which is found in the cerebral cortex and cardiac tissue and appears to be involved in centrally mediated pain.

For this report, we defined the terms "selective NSAIDs" or "COX-2 selective NSAIDs" as drugs in the "coxib" class (celecoxib, rofecoxib, valdecoxib, etoricoxib, lumiracoxib). We defined "partially selective NSAIDs" as other drugs shown to have partial in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam). Aspirin differs from other NSAIDs because it irreversibly inhibits platelet aggregation, and the salicylic acid derivatives (aspirin and salsalate)

were considered a separate subgroup. We defined "nonaspirin, nonselective NSAIDs" or simply "nonselective NSAIDs" as "all other NSAIDs."

This report summarizes the available evidence comparing the benefits and harms of analgesics in the treatment of osteoarthritis.

Oral agents include:

- Aspirin
- Aacetaminophen
- Celecoxib
- Choline magnesium trisalicylate
- Chondroitin
- Diclofenac
- Diflunisal
- Etodolac
- Etoricoxib[1]
- Fenoprofen
- Flurbiprofen
- Glucosamine
- Ibuprofen
- Indomethacin
- Ketoprofen
- Ketoprofen ER
- Ketorolac
- Lumiracoxib[1]
- Meclofenamate sodium
- Mefenamic acid
- Meloxicam
- Nabumetone
- Naproxen
- Oxaprozin
- Piroxicam
- Rofecoxib[1]
- Salsalate
- Sulindac
- Tenoxicam[1]
- Tiaprofenic acid[1]
- Tolmetin
- Valdecoxib[1]

[1] These drugs are currently not approved by the FDA for use in the United States (etoricoxib, lumiracoxib, tenoxicam, tiaprofenic acid) or have been withdrawn from the market (rofecoxib and valdecoxib).

Questions addressed in this report are:

1. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? *(Note: The only benefits considered under this question are improvements in osteoarthritis symptoms from long-term use. Evidence of harms associated with NSAID use include long-term studies of these drugs for treating osteoarthritis or rheumatoid arthritis and for cancer prevention.*

2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups of patients?

   - Demographic subgroups include age, sex, and race.

   - Coexisting diseases include hypertension, edema, ischemic heart disease, heart failure; peptic ulcer disease; history of previous bleeding due to NSAIDs.

- Concomitant medication use includes anticoagulants.

3. What are the comparative effects of coprescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?
4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations? Topical preparations include: capsaicin, diclofenac, ibuprofen, ketoprofen, and salicylate.

A summary of the findings is shown in Table A.

Conclusions

Oral NSAIDs

Benefits: improvements in osteoarthritis symptoms

- **Nonselective NSAID vs. another nonselective NSAID**
  - Many trials found no clear differences between various nonaspirin, nonselective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac) in efficacy for pain relief or improvement in function.
  - In one short-term trial, salsalate and aspirin did not differ significantly in efficacy for pain relief or symptom improvement.
  - No studies evaluated the comparative efficacy of salsalate or aspirin vs. a nonaspirin NSAID.
- **COX-2 selective (NSAID) vs. nonselective NSAID**
  - COX-2 selective NSAIDs and nonselective NSAIDs did not clearly differ in efficacy for pain relief, based on many good-quality, published trials.
- **COX-2 selective NSAID vs. different COX-2 selective NSAID**
  - Celecoxib and rofecoxib did not differ significantly in efficacy for pain relief at commonly used and comparable doses, based on consistent evidence from six good-quality trials.
  - No studies compared efficacy of COX-2s other than celecoxib and rofecoxib.

Harms: gastrointestinal (GI) and cardiovascular (CV)

- **Rofecoxib vs. nonselective NSAID**

- In the only large, long-term trial (VIGOR), rofecoxib 50 mg daily caused fewer serious ulcer complications than naproxen 1,000 mg daily in patients with rheumatoid arthritis but also significantly increased the risk of myocardial infarction. The overall rate of serious adverse events was higher with rofecoxib than with naproxen.

    - There were about 16 fewer symptomatic ulcers, including 5.2 fewer serious GI complications, for every 1,000 patients treated with rofecoxib vs. naproxen after a median of 9 months of treatment.

    - There were 3.0 additional myocardial infarctions for every 1,000 patients treated with rofecoxib compared to naproxen in VIGOR.

- Rofecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of randomized controlled trials (RCTs).

    - About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with rofecoxib compared to placebo in the systematic review.

- Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks.

- **Celecoxib vs. nonselective NSAID or placebo**

    - It is not clear whether celecoxib has fewer potential harms than nonselective NSAIDs when used longer than 3-6 months. In the only large, published trial (CLASS), celecoxib at 800 mg daily did not decrease predefined serious ulcer complications overall compared with diclofenac and ibuprofen; the risk of serious GI events was lower than with ibuprofen, but not diclofenac, at 6 months in patients who did not use aspirin; and there was no reduction in serious GI events at the end of followup. The overall rate of serious adverse events with celecoxib was similar to the rate with ibuprofen and diclofenac.

    - In fair-quality meta-analyses of arthritis trials, most of which evaluated short-term use, celecoxib caused fewer ulcer complications than nonselective NSAIDs and did not increase the risk of myocardial infarction.

    - Celecoxib 400 mg twice daily was associated with an increased risk of serious CV events (CV death or myocardial infarction) relative to placebo in a long-term trial of polyp prevention.

    - Celecoxib was associated with an increased risk of myocardial infarction relative to placebo in the most comprehensive systematic review of RCTs. Most of the

CV events with celecoxib were reported in two large polyp-prevention trials evaluating 200 mg or 400 mg twice daily, or 800 mg once daily.

- About 3.5 additional myocardial infarctions occurred for every 1,000 patients treated for 1 year with celecoxib compared to placebo.

- **Valdecoxib vs. nonselective NSAID or placebo**

  - Valdecoxib was associated with a lower risk of upper GI complications compared with diclofenac, ibuprofen, or naproxen in two fair-quality meta-analyses of published and unpublished trials.

  - There have been too few events reported in RCTs of patients with chronic conditions to accurately assess CV risk associated with valdecoxib.

  - Two short-term trials in a high-risk post-coronary-artery-surgery setting found that valdecoxib was associated with a two- to threefold higher risk of CV events compared with placebo.

  - Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk.

- **Etoricoxib vs. nonselective NSAID**

  - Etoricoxib was associated with fewer GI adverse events (perforations, symptomatic ulcers, and bleeds) than nonselective NSAIDs in a fair-quality meta-analysis of 10 trials.

  - In primarily short-term trials, systematic reviews of RCTs suggest that etoricoxib has a similar CV safety profile compared to other NSAIDs, with the possible exception of naproxen. Definitive conclusions are not possible because of small numbers of CV events.

- **Lumiracoxib vs. nonselective NSAID**

  - Results from one large trial (TARGET) found fewer adverse GI events with lumiracoxib than with naproxen and ibuprofen.

  - There was no statistically significant difference in rates of serious CV events between lumiracoxib relative to naproxen or ibuprofen in TARGET.

  - Too few events have been reported in RCTs to accurately assess CV risk associated with lumiracoxib.

- **Partially selective NSAID vs. nonselective NSAID**

- Meloxicam: There were no significant differences in risks of serious GI events in several meta-analyses of up to 28 primarily short-term clinical trials, and no difference in CV risk in three observational studies.

- Nabumetone or etodolac: There was insufficient evidence to make reliable judgments about relative GI safety and no evidence on CV safety.

- **Nonselective NSAID vs. nonselective NSAID or any COX-2 selective NSAID**

  - No clear difference in GI safety was found among nonselective NSAIDs at commonly used doses.

  - The CV safety of naproxen was moderately superior to that of any COX-2 selective NSAID in a large systematic review of RCTs.

    - There were 3.3 additional myocardial infarctions for every 1,000 patients treated with any COX-2 inhibitor instead of naproxen for 1 year.

  - The CV safety of nonselective NSAIDs other than naproxen (data primarily on ibuprofen and diclofenac) was similar to that of COX-2 selective NSAIDs in a large systematic review.

  - In indirect analyses, naproxen was the only nonselective NSAID associated with neutral CV risk relative to placebo.

- **Aspirin**

  - Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds compared to placebo or nonuse when given in long-term prophylactic doses.

  - There is insufficient evidence to assess the balance of GI and CV safety of higher dose aspirin as used for pain relief compared with nonaspirin NSAIDs.

- **Salsalate**

  - Salsalate was associated with a lower risk of adverse events than other selective and nonselective NSAIDs using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDS.

  - Almost no data are available on CV safety.

Harms: mortality

- Individual trials were not large enough to detect differences in mortality between the

included drugs.

- One meta-analysis of celecoxib found no difference between celecoxib and nonselective NSAIDs, but there were few events.
- In one fair-quality cohort study, nabumetone was associated with a lower risk of all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.

Harms: hypertension, congestive heart failure (CHF), edema, and impaired renal function

- All NSAIDs and COX-2 inhibitors can cause or aggravate these conditions.

- There is good evidence from short-term trials that, on average, nonselective NSAIDs raise mean blood pressure by about 5.0 mm Hg (95-percent confidence interval [CI] 1.2 to 8.7). However, similar average blood pressure changes may not necessarily correspond with similar likelihoods of an event requiring withdrawal, medication change, or other clinical consequences.

- Evidence from good-quality observational studies suggests that rofecoxib is associated with greater risks of hypertension, CHF, and edema than celecoxib. Indirect evidence from various meta-analyses of either rofecoxib or celecoxib vs. nonselective NSAIDs are consistent with these findings. Direct randomized trial evidence, however, is limited in quantity and difficult to interpret because of possible non-equivalent dosing of drugs. Evidence regarding the comparative risk of renal dysfunction for celecoxib and rofecoxib is sparse.

- There was weak evidence that aspirin and sulindac have less hypertensive effect than other nonselective NSAIDs.

- There were no clear differences among other selective or nonselective NSAIDs for these adverse events.

Harms: hepatotoxicity

- Clinically significant hepatotoxicity was rare.

- Among currently marketed NSAIDs, only diclofenac was associated with a significantly higher rate of liver-related discontinuations compared with placebo (1 additional case for every 53 patients treated with diclofenac).

Tolerability

- Relative to nonselective NSAIDs, COX-2 selective and partially selective NSAIDs were better or similarly tolerated and aspirin was less well tolerated.

- There were no clear differences in tolerability among COX-2 selective or

nonselective NSAIDs.

- Uncertainty remains regarding the comparative tolerability of salsalate and nonselective NSAIDs. Available evidence is somewhat sparse and mixed, with two of three short-term trials suggesting salsalate is less well tolerated than nonselective NSAIDs and older, flawed observational studies suggesting that salsalate is less toxic than nonselective NSAIDs.

Other oral agents: benefits and harms

- **Acetaminophen**
  - Acetaminophen was modestly inferior to NSAIDs for pain and function in four systematic reviews.
    - Pain severity ratings averaged less than 10 points higher for acetaminophen compared to NSAIDs on 100-point visual analog scales.
  - Compared with NSAIDs, acetaminophen had fewer GI side effects (clinical trials data) and serious GI complications (observational studies).
  - Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies).
  - One good-quality, prospective observational study found an increased risk of CV events with heavy use of acetaminophen that was similar to the risk associated with heavy use of NSAIDs.
  - Acetaminophen at therapeutic doses does not appear to be associated with an increased risk of hepatotoxicity compared to nonuse in patients without underlying liver disease.
- **Glucosamine and chondroitin**
  - In one large, good-quality trial the combination of pharmaceutical-grade glucosamine hydrochloride plus chondroitin (not currently available in the United States) was not superior to placebo among all patients studied. Neither glucosamine nor chondroitin alone was superior to placebo. In an analysis of a small subgroup of patients with at least moderate baseline pain, there was a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis.
  - Systematic reviews of older trials found glucosamine modestly superior to oral NSAIDs and placebo in most trials, but there was some inconsistency between trials, most trials had some flaws, and results may not be directly applicable to the United States because the positive trials primarily evaluated pharmaceutical-grade glucosamine available in Europe.

- Only 2 of 20 placebo-controlled trials assessed effects of glucosamine on radiologic disease progression. One fair- and one good-quality trial found pharmaceutical-grade glucosamine superior to placebo for progression of knee joint space narrowing over 3 years.

- Glucosamine and chondroitin were generally well tolerated and no serious adverse events were reported in clinical trials.

Effect of dosage and duration of treatment on the benefits and harms of oral medication use

- We found no studies evaluating the GI or CV safety of alternative dosing strategies (such as alternate day dosing, once daily versus twice daily dosing, or periodic drug holidays).

- The risk of GI bleeding increases with higher doses of nonselective NSAIDs.

- The most comprehensive systematic review of RCTs found no clear association between duration of exposure and CV risk of COX-2 inhibitors. However, estimates of CV risk with shorter duration of exposure are imprecise due to low numbers of events.

- The most comprehensive systematic review of RCTs found higher doses of celecoxib associated with increased CV risk, but could not determine the effects of dose on CV risk associated with rofecoxib due to low numbers of events at lower doses. Most trials of nonselective NSAIDs involved high doses.

Differences in demographic and clinical subgroups

- GI and CV complication rates are higher among older patients and those with predisposing comorbid conditions, but there is no evidence that the relative safety of different NSAIDs varies according to baseline risk.

    - Compared to nonuse of NSAIDs, one additional death per 1 year of use occurred for every 13 patients treated with rofecoxib, 14 with celecoxib, 45 with ibuprofen, and 24 with diclofenac in one large, population-based observational study of high-risk patients with acute myocardial infarction.

- There is no evidence that the comparative safety or efficacy of specific selective or nonselective NSAIDs varies depending on age, gender, or racial group, although data are sparse.

- Among patients who had a recent episode of upper GI bleeding, there is good evidence that rates of recurrent ulcer bleeding are high (around 5 percent after 6 months) in patients prescribed celecoxib or a nonselective NSAID plus a PPI.

Concomitant anticoagulant use

- Concomitant use of anticoagulants (e.g., warfarin) and any nonselective NSAID increases the risk of GI bleeding three- to sixfold compared to anticoagulants alone.
- Reliable conclusions about the safety of selective NSAIDs used with anticoagulants are not possible due to flaws in existing observational studies, although there are case reports of serious bleeding events, primarily in the elderly.

Concomitant aspirin use

- In the CLASS studies, there was no difference in rates of ulcer complications between celecoxib and nonselective NSAIDs in the subgroup of patients who took aspirin.

- Concomitant low-dose aspirin use increased the rate of endoscopic ulcers by about 6 percent in both patients on celecoxib and those on nonselective NSAIDs in one meta-analysis.

- Rofecoxib plus low-dose aspirin or ibuprofen alone were associated with similar risks of endoscopic ulcers (16-17 percent), which were significantly higher than those for placebo (6 percent) or aspirin alone (7 percent).

- The most comprehensive systematic review of RCTs found that compared to nonuse of aspirin, concomitant aspirin use did not ameliorate the increased risk of vascular events associated with COX-2 selective NSAIDs.

Effects of coprescribing H2-antagonists, misoprostol, or PPIs

- Consistent evidence from good-quality systematic reviews and numerous clinical trials found coprescribing of PPIs to be associated with the lowest rates of endoscopically detected duodenal ulcers relative to gastroprotective agents.

- Coprescribing of misoprostol is associated with similar rates of endoscopically detected gastric ulcers as coprescribing of PPIs.

- While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of perforation, obstruction, or bleeding, there is a high rate of withdrawals due to adverse GI symptoms.

- The risk of endoscopic duodenal ulcers for *standard*-dose H2 blockers was lower than placebo, similar to misoprostol, and higher than omeprazole. Standard dosages of H2 blockers were associated with no reduction of risk for gastric ulcers relative to placebo.

- *Double (full)* dose H2 blockers were associated with a lower risk of endoscopic gastric and duodenal ulcers relative to placebo. It is unknown how full-dose H2 blockers compare to other antiulcer medications because head-to-head trials are lacking.

Comparison of oral medications with topical preparations

- **Topical NSAIDs: efficacy**
    - Studies of topical NSAIDs typically evaluated proprietary formulations not approved by the FDA.
    - Topical NSAIDs were similar to oral NSAIDs for pain relief in trials primarily of patients with osteoarthritis of the knee, with topical diclofenac (often with dimethyl sulphoxide [DMSO], a drug not approved for use in humans in the United States) best studied.
    - Topical ibuprofen was superior to placebo in several trials.
- **Topical NSAIDs: safety**
    - Consistent evidence from good-quality trials, systematic reviews, and observational studies found topical NSAIDs to be associated with increased local adverse events compared with oral NSAIDs.
    - Total adverse events and withdrawal due to adverse events were similar.
    - Data from one good-quality trial found topical NSAIDs superior to oral NSAIDs for GI events, including severe events, and changes in hemoglobin.
- **Topical salicylates and capsaicin**
    - Topical salicylates were no better than placebo in higher quality placebo-controlled trials.
    - Compared to placebo, one additional patient achieved pain relief for every eight that used topical capsaicin in a good-quality meta-analysis, but capsaicin was associated with increased local adverse events and withdrawals due to adverse events.

Balance of evidence and harms

Each of the analgesics evaluated in this report was associated with a unique set of benefits and risks. Each was also associated with gaps in the evidence necessary to determine the true balance of benefits vs. harms. The role of selective and nonselective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence vary, no currently available analgesic reviewed in this report was identified as offering a clear overall advantage compared with the others. This is not surprising, given the complex tradeoffs between the many benefits (pain relief, improved function,

improved tolerability, and others) and harms (CV, renal, GI, and others) involved.

Individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of an increase in CV risk, for example, could be an acceptable tradeoff for some patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and CV events), comorbid conditions, and concomitant medication use (such as aspirin and anticoagulation medications). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant tradeoffs.

Remaining Issues

- The CV safety of nonselective NSAIDs has not been well studied in large, long-term clinical trials. Naproxen, in particular, may be associated with fewer CV risks than other NSAIDs and should be investigated in long-term, appropriately powered trials.

- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms but have generally had a narrow focus on single adverse events. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall tradeoffs between benefits and harms.

- The CV risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.

- Meta-analyses of the risks associated with selective COX-2 inhibitors need to continue to assess the effects of dose and duration as more data become available; current estimates of risks at lower doses and with shorter duration of exposure are less precise than estimates at higher doses and longer duration of exposure because of small numbers of events.

- Large, long-term trials of the GI and CV safety associated with full-dose aspirin, salsalate, or acetaminophen compared with nonaspirin NSAIDs or placebo are lacking. Recent observational data suggesting an increased CV risk with heavy use of acetaminophen highlight the need for long-term, appropriately powered clinical trials.

- Given the large number of patients who meet criteria for aspirin prophylaxis for CV events, more trials evaluating the dose-related effects of aspirin 50-1500 mg on GI benefits and CV safety are needed.

- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once daily versus twice daily dosing

of certain COX-2 inhibitors could reduce CV risk, this hypothesis has not yet been tested in a clinical trial.

- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical-grade glucosamine not available in the United States and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations of glucosamine and chondroitin with oral NSAIDs are needed, as these are likely to remain available even if the FDA approves pharmaceutical-grade formulations.

- No topical NSAIDs are FDA approved in the United States, yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO, which is not approved in the United States for use in humans. Cohort studies using large observational databases may be required to adequately assess CV risk.

As this report was going to press, two relevant meta-analyses on risks associated with NSAIDs were published. We were unable to fully incorporate these studies into this report, but found their results generally consistent with our conclusions:

- A fair-quality meta-analysis of arrhythmia and renal event (peripheral edema, hypertension, or renal dysfunction) risk from 114 randomized trials of COX-2 selective NSAIDs found rofecoxib associated with increased risks of arrhythmia (primarily ventricular fibrillation, cardiac arrest, or sudden cardiac death) and renal dysfunction (peripheral edema, hypertension, or renal dysfunction) relative to control treatments (placebo, other NSAIDs, or mixed/other) . The increased risk was equivalent to approximately 1.1 additional arrhythmia events per 1,000 patients treated with rofecoxib. Celecoxib was associated with lower risks of renal dysfunction and hypertension than control treatments, although there was no difference for the pre-specified, primary composite renal outcome of peripheral edema, hypertension, renal dysfunction or arrhythmia. There was no clear association between other COX-2 inhibitors (valdecoxib/parecoxib, etoricoxib, or lumiracoxib) and either arrhythmia or renal events (no arrhythmia events reported with lumiracoxib).

- A good-quality meta-analysis of cardiovascular risk (primarily myocardial infarction) from 23 observational studies was largely consistent with our qualitative assessment of the observational literature. It found rofecoxib associated with a dose-dependent, increased risk of cardiovascular events that was detectable during the first month of treatment. Of the other NSAIDs, diclofenac was associated with the highest risk, followed by indomethacin and meloxicam. Celecoxib, naproxen, piroxicam, and ibuprofen were not associated with increased risks. Assessments of increased risk were modest (relative risks all <2.0), and all of the main analyses were associated with substantial between-study heterogeneity.

Table A. Summary of Findings on Comparative Effectiveness and Safety of Analgesics for Osteoarthritis, with Strength of Evidence

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
COX-2 selective NSAIDs	▪ Good evidence COX-2-selective NSAIDs are comparable in efficacy (pain relief) to nonselective NSAIDs. ▪ Good evidence COX-2 selective NSAIDs are comparable in efficacy to each other.	▪ **GI:** Fair to good evidence of fewer serious GI events with COX-2 selective NSAIDs compared to nonselective NSAIDs, at least in the first 6 months of treatment. ▪ **CV:** Comparative data on CV risks of COX-2 selective vs. nonselective and partially selective NSAIDs are sparse, with a few exceptions (see below). Fair evidence that COX-2 selective NSAIDs are associated with increased risks of serious CV events (primarily myocardial infarction) compared to placebo. CV risks may increase with greater dosages and durations of treatment, but estimates of risks at lower doses and with shorter durations of treatment are imprecise due to small numbers of events. o Rofecoxib was withdrawn from the market in September 2004, primarily because of CV risks. o Cautions about CV risk apply primarily to rofecoxib and celecoxib, as CV safety data are less precise (due to small numbers of events) for valdecoxib, etoricoxib, and lumiracoxib. ▪ **Other** o Valdecoxib was withdrawn from the market due to life-threatening skin reactions and increased CV risk. o Fair evidence suggests that rofecoxib is associated with greater risk of hypertension, CHF, edema, and cardiorenal events than celecoxib.	▪ Good evidence that risk of GI bleeding and CV events increases with age. ▪ Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. ▪ Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities.
NSAIDs : nonselective (including naproxen), partially selective	▪ Good evidence nonselective and partially selective NSAIDs are comparable in efficacy to each other.	▪ **GI :** Good evidence that all nonselective NSAIDs are associated with comparable, dose-dependent increases in risk of serious GI events compared to nonuse. Good evidence that coprescription of misoprostol or PPIs can attenuate this risk, but misoprostol is less well tolerated. o No clear evidence (fair for meloxicam and poor for etodolac and nabumetone) that partially selective NSAIDs are associated with decreased risk relative to nonselective NSAIDs. ▪ **CV :** Data on CV risks of nonselective and partially selective NSAIDs are sparse, with a few exceptions: o Fair evidence that high doses of ibuprofen and diclofenac carry similar risks of serious CV events compared to COX-2 selective NSAIDs. o Fair evidence that naproxen is associated with a lower risk of CV events than COX-2 selective NSAIDs and no excess risk compared to placebo. ▪ **Other:** Fair evidence that diclofenac is associated with higher rates of aminotransferase elevations than other NSAIDs.	▪ Good evidence that risk of GI bleeding and CV events increases with age. ▪ Good evidence that risk of GI bleeding is greater in patients with prior bleeding episodes. ▪ Fair evidence that risks of CV and renal events are higher in patients with cardiac and renal comorbidities. ▪ Fair evidence that using NSAIDs concomitantly with anticoagulants increases GI bleeding risk three- to sixfold.

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
Aspirin/ salsalate	▪ No evidence comparing efficacy of aspirin or salsalate to COX-2s or NSAIDs.	▪ Good evidence that aspirin 50-1500 mg (for thrombotic event prophylaxis) is associated with greater risks of serious GI events compared to placebo or when added to warfarin. ▪ Good evidence that low-dose aspirin is effective for preventing CV events. ▪ Insufficient evidence to assess GI and CV risks associated with higher doses of aspirin for pain control or with salsalate.	▪ Good evidence that concomitant use of aspirin attenuates or eliminates the GI benefits of COX-2 selective NSAIDs. ▪ Fair evidence that concomitant use of low-dose aspirin does not eliminate CV risks when added to NSAIDs .
Acetaminophen	▪ Good evidence that acetaminophen is modestly inferior in efficacy compared to NSAIDs.	▪ Good evidence of lower risk of GI complications with acetaminophen compared to NSAIDs. ▪ Fair evidence of increased risk of blood pressure and renal dysfunction with acetaminophen compared to nonuse. ▪ Poor evidence (a single observational study) that heavy use of acetaminophen carries a similar CV risk compared to heavy use of NSAIDs.	None
Glucosamine (pharmaceutical grade)/ chondroitin	▪ Fair evidence (some inconsistency between clinical trials) that pharmaceutical-grade glucosamine and chondroitin are not more effective than placebo in unselected patients, including one recent, large, good-quality trial finding no beneficial effects from glucosamine or chondroitin alone or in combination. In an analysis of a small subgroup of patients with at least moderate baseline pain in the latter trial, there appeared to be a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis. ▪ Fair evidence of no clear difference in efficacy between pharmaceutical-grade glucosamine or chondroitin and NSAIDs. ▪ No studies compared glucosamine or chondroitin to acetaminophen.	▪ Good evidence that glucosamine and chondroitin are well tolerated and do not appear to be associated with serious adverse events.	None

Treatment	Benefits: symptom relief	Harms: gastrointestinal, cardiovascular, and other	Special considerations in subgroups
Topical NSAIDs	▪ Good evidence they are comparable to oral NSAIDs for pain relief in trials primarily of patients with knee osteoarthritis. o Most trials of topical NSAIDs evaluate proprietary formulations not available in the United States.	▪ Good evidence that topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. ▪ Good evidence that topical and oral NSAIDs are comparable in rates of total adverse events and withdrawals due to adverse events. ▪ Good evidence that topical NSAIDs are associated with fewer GI events, including severe events, and changes in hemoglobin compared to oral NSAIDs.	None
Topical salicylates and capsaicin	▪ Fair evidence that capsaicin, but not topical salicylates are superior for pain relief compared to placebo.	▪ Good evidence that topical capsaicin is associated with increased local adverse events and withdrawals due to adverse events compared to placebo.	None

Abbreviations: CHF = congestive heart failure; COX = cyclo-oxygenase; CV = cardiovascular; GI = gastrointestinal; NSAID=nonsteroidal antiinflammatory drug; PPI=proton pump inhibitor.

Chapter 1. Introduction

Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life.[2] Among U.S. adults aged 30 or older, approximately 6% have symptomatic osteoarthritis of the knee, and 3% have symptomatic osteoarthritis of the hip.[3] Osteoarthritis increases with age, with the incidence and prevalence increasing 2- to 10-fold from age 30 to 65, and continues to increase after age 65.[4] Osteoarthritis accounts for more disability in walking, stair climbing, and other tasks requiring use of the lower extremities than any other disease, particularly in the elderly.[5] The total costs for arthritis, including osteoarthritis, may be greater than 2% of the gross domestic product,[3] with more than half of these costs related to work loss.[5]

In addition to non-pharmacologic interventions (such as physical therapy, weight reduction, and exercise), numerous medications and over-the-counter supplements are available to treat pain and potentially improve functional status in patients with osteoarthritis. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may also vary for individual drugs within a class. Oral medications commonly used to treat osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (Appendix A). Many are available at lower over-the-counter and higher prescription doses. Commonly used supplements sold over-the-counter and not regulated as pharmaceuticals by the FDA include glucosamine and chondroitin. Topical agents frequently used by patients with osteoarthritis are rubefacients (including capsaicin), NSAIDs, and other miscellaneous preparations.[6] Opioid medications are also used for patients with chronic pain, especially if it is refractory to other therapies, but are not recommended for first-line treatment for osteoarthritis or other conditions because of risks of addiction, tolerance, diversion, and other adverse events.[7, 8]

NSAIDs exert analgesic, anti-inflammatory, and anti-pyretic effects by blocking *cyclo-oxygenases (COX)*, enzymes that are needed to produce *prostaglandins*. Understanding of the pharmacology of NSAIDs continues to evolve, but it is now thought that most NSAIDs block three different COX isoenzymes, known as COX-1, COX-2, and COX-3. COX-2, found in joint and muscle, contributes to pain and inflammation. Because they block COX-2, non-steroidal anti-inflammatory drugs reduce pain compared to placebo in patients with arthritis,[9] low back pain,[10] minor injuries, and soft tissue rheumatism. Less is known about COX-3, which has been found in the cerebral cortex and cardiac tissue and appears to have effects on centrally-mediated pain.[1]

NSAIDs are also associated with important adverse effects. NSAIDs cause gastrointestinal (GI) bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. In the 1990s in the United States, nonaspirin NSAIDs are estimated cause 32,000 hospitalizations and 3,200 deaths annually from GI bleeding.[11] A risk analysis[12] based on a retrospective case-control survey of emergency admissions for upper GI disease in two United Kingdom general hospitals provided useful estimates of the frequency of serious GI complications from NSAIDs.[13] In people taking NSAIDs, the 1-year risk of serious GI bleeding ranges from 1 in 2,100 in adults under age 45 to 1 in 110 for adults over age 75, and the risk of death ranges from 1 in 12,353 to 1 in 647 (Table 1). In addition to age, prednisone use, disability level, and previous NSAID-induced GI symptoms are risk factors for GI bleeding.

Table 1. One year risk of GI bleeding due to NSAID

Age range (years)	Chance of GI bleed due to NSAID	Chance of dying from GI bleed due to NSAID
	Risk in any one year is 1 in:	
16-45	2100	12,353
45-64	646	3800
65-74	570	3353
≥ 75	110	647

Data are from Blower,[13] recalculated in Moore[12] and in Bandolier[14]

NSAIDs differ in their selectivity for COX-2—how much they affect COX-2 relative to COX-1. Theoretically, an NSAID that blocks COX-2 but not COX-1 might reduce pain and inflammation in joints but leave the stomach lining alone. Appendix B[15] summarizes the NSAIDs and their selectivity based on assay studies (done in the laboratory instead of in living patients). The table gives an idea of how widely NSAIDs vary in their selectivity, but should be interpreted with caution. Different assay methods give different results, and assay method may not reliably predict what will happen when the drug is given to patients. Clinical studies, rather than these assay studies, are the best way to determine whether patients actually benefit from using more selective NSAIDs.

In addition to their propensity to cause GI bleeding, NSAIDs are also associated with adverse effects on blood pressure, renal function, and fluid retention. Mechanisms may involve attenuation of prostaglandin-mediated vasodilation, promotion of sodium and water retention, increased vascular resistance, and increased renal endothelin-1 synthesis.[16-18]

An association between selective COX-2 inhibitors and increased rates of myocardial infarction was first observed in the large, pivotal Vioxx Gastrointestinal Outcomes Research (VIGOR) trial comparing high-dose rofecoxib (50 mg) to naproxen 1000 mg.[19] Reasons for the increase in thromboembolic cardiovascular event risk are complex and not completely understood, but may be related in part to suppression of endothelial-derived prostaglandin I2 formation by selective COX-2 inhibition, in the setting of unaffected platelet production of pro-thrombotic COX-1 mediated thromboxane A2.[20] Blood pressure elevations associated with COX-2 inhibitors may also play a role in increasing cardiovascular risk.[21] On September 30, 2004, rofecoxib was withdrawn from the market after a long-term polyp prevention trial found an increased risk of myocardial infarction compared with placebo.[22] On December 9, 2004, the US Food and Drug Administration issued a black-box warning for valdecoxib for life-threatening skin reactions and increased cardiovascular risk. This drug was subsequently also withdrawn voluntarily by the manufacturer.[23]

Aspirin, or acetylsalicylic acid, has long been known to have analgesic, anti-pyretic, and anti-inflammatory effects.[24] It is thought to be the most consumed medicinal drug in the world. Like the non-aspirin NSAIDs, aspirin's effects are due to blockade of cyclo-oxygenases. However, an important distinction between aspirin and non-aspirin NSAIDs is that aspirin also induces irreversible functional defects in platelets (although non-aspirin NSAIDs also have effects on platelet aggregation, they are short-lived). Because of these antiplatelet effects, low-dose aspirin is also used prophylactically to reduce the risk of thrombotic events.[25] However, even at doses of 325 mg daily or lower, the potential cardiovascular benefits must be balanced against dose-dependent risk of aspirin-induced adverse GI events. Salsalate, a nonacetylated salicylate, is a prodrug of salicylic acid, the active metabolite of aspirin. However, salsalate is considered a relatively weak inhibitor of cyclo-oxygenases.[26]

Acetaminophen (also known as paracetamol) is an anti-pyretic and analgesic medication that

is not thought to have significant anti-inflammatory properties. Although its mechanism of inducing analgesia is still not completely understood, it is thought to work in part by indirectly decreasing production of prostaglandins through inhibitory effects involving COX-2.[16, 27] Acetaminophen is frequently recommended as a first line agent for osteoarthritis and other pain conditions because of its perceived favorable safety profile—particularly with regard to ulcer risk.[28]

Chondroitin sulfate and glucosamine sulfate are natural compounds found in cartilage. Both are marketed to patients who have osteoarthritis. The precise mechanisms of action are unknown, but may involve promoting maintenance and repair of cartilage. Glucosamine, for example, has been shown to increase proteoglycan synthesis.[29] In the European Union countries, glucosamine is available as a prescription drug manufactured by the Rotta Pharmaceutical Company. In the U.S., by contrast, glucosamine and chondroitin are considered dietary supplements and are not regulated as pharmaceuticals. Adequate standardization of glucosamine and chondroitin preparations is a significant concern. It has been shown that the actual content often varies substantially from what is stated on the label.[30] Such inconsistencies may have implications on estimates of efficacy and safety for different commercial preparations.

Topical administration of NSAIDs could theoretically result in local analgesic and anti-inflammatory effects by direct absorption through the skin, with reduced systemic adverse events compared with oral administration.[31] Experimental studies indicate that topical administration is associated with substantially higher concentrations of NSAIDs in soft tissue (particularly meniscus and cartilage) and lower peak plasma concentrations compared with oral administration.[6] For a topical NSAID to be effective, it has to reach the inflamed tissue in sufficient concentrations to produce analgesic and anti-inflammatory activity. The solubility of specific NSAIDs varies considerably, and is also affected by the carrier or formulation used.[31] Superior *in vivo* permeability characteristics, however, may not predict clinical effectiveness.

In contrast to topical NSAIDs, whose mechanism of action involves inhibition of cyclo-oxygenase, topical rubefacients are thought to relieve pain through counter irritation.[6, 32] Although the mechanism of action of topical preparations containing salicylate esters is unclear, they are now usually classified as rubefacients rather than topical NSAIDs because they may not work via inhibition of cyclo-oxygenase.[6, 33] Capsaicin, which is also often classified as a rubefacient, is derived from the hot chili pepper (*Capsicum* species). It is applied topically and thought to work by stimulating the release of substance P and other neuropeptides from sensory nerve endings.[34] Although this release can initially lead to burning and pain, analgesia occurs after repeated and continued application, as substance P becomes depleted. Although a wide variety of other rubefacients are available, only topical salicylates and capsaicin were included in this review.

The purpose of this report was to assess the comparative efficacy and safety of non-opioid oral medications (selective and non-selective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Scope and Key Questions

1. What are the comparative benefits and harms of treating osteoarthritis

with oral medications or supplements? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? *(Note: This question addresses the therapeutic benefits of long-term use for the condition osteoarthritis. However, the question does address all harms associated with NSAID use, including use for other labeled indications such as the treatment of rheumatoid arthritis.)*

Oral NSAIDs include:

- aspirin
- celecoxib
- choline magnesium trisalicylate
- diclofenac
- diflunisal
- etodolac
- etoricoxib*
- fenoprofen
- flurbiprofen
- ibuprofen
- indomethacin
- ketoprofen
- ketoprofen ER
- ketorolac
- lumiracoxib*
- meclofenamate sodium
- mefenamic acid
- meloxicam
- nabumetone
- naproxen
- oxaprozin
- piroxicam
- rofecoxib*
- salsalate
- sulindac
- tenoxicam*
- tiaprofenic acid*
- tolmetin
- valdecoxib*

** These drugs are currently not approved (etoricoxib, lumiracoxib, tenoxicam, tiaprofenic acid) for use in the United States by the FDA or have been withdrawn from the market (rofecoxib and valdecoxib)*

Other oral agents include acetaminophen, chondroitin, and glucosamine. See Appendix A for a detailed listing of pharmacokinetics, indications, and recommended dosing information for all included drugs. Appendix C shows low, medium and high doses for the more commonly used NSAIDs.

For this report, we defined the terms "selective NSAID" or "COX-2 selective NSAID" as drugs in the "coxib" class (e.g. celecoxib, rofecoxib, and valdecoxib). We grouped etodolac, nabumetone, and meloxicam into a separate category that we referred to as "partially selective NSAIDs," to explore how in vitro differences in COX-2 selectivity might translate into clinical differences in safety. The salicylic acid derivatives aspirin and salsalate were also considered a separate subgroup. We defined "non-aspirin, non-selective NSAIDs" or simply "non-selective NSAIDs" as all other NSAIDs. We included evidence on the efficacy and safety of the COX-2 inhibitor rofecoxib, even though it is no longer available in the U.S., because it was the first drug to be associated with cardiovascular risks and therefore provides important historical context and illustrates important issues to consider when evaluating the risks and benefits of selective and non-selective NSAIDs. For other COX-2 inhibitors not approved by the FDA for use in the U.S.

(lumiracoxib and etoricoxib) or withdrawn from the market (valdecoxib), we focused only on evidence regarding long-term, serious GI and CV adverse events, which is likely to be the most important factor driving future decisions regarding their use.

"Benefits" include relief of pain and osteoarthritic symptoms and improved functional status. The main outcome measures for this review were pain, functional status, and discontinuations due to lack of efficacy. Frequently used outcome measures include visual and categorical pain scales:[35]

Visual analogue scale (VAS): Using VAS, patients indicate their level of pain, function, or other outcome by marking a scale labeled with numbers (such as 0 to 100) or descriptions (such as "none" to "worst pain I've ever had"). An advantage of VAS is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient's subjective experience of pain. This poses a challenge in objectively comparing different patients' scores, or even different scores from the same patient.

Categorical pain scales consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must chose among categories that may not accurately describe their pain. A variety of disease-specific and non-specific scales are used to assess these outcomes in patients with osteoarthritis. Commonly used categorical pain scales include:

- The *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC), a 24-item, disease-specific questionnaire used to assess the functional status of patients with osteoarthritis of the knee and hip. A lower score indicates better function.[36]

- The *Medical Outcomes Short Form-36 (SF-36)* health survey, a commonly used general instrument for measuring health-related quality of life across different diseases.[37]

- *Patient Global Assessment of Disease Status* and *Investigator Global Assessment of Disease Status.* The patient or investigator answers questions about the overall response to treatment, functional status, and pain response, using a VAS or categorical scale.

- *American College of Rheumatology (ACR) criteria* measure disease activity and response to treatment. ACR 20, ACR 50, or ACR 70 reflect either an improvement to the 20%, 50%, or 70% level in the parameters outlined.

Another method for measuring outcomes is classifying patients dichotomously as "responders" or "non-responders." Responders are often defined as patients with at least a 50% improvement in pain or function. The *Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria,* for example, were developed through a consensus process and classifies patients as responders if they meet specific pre-defined criteria (>=50% improvement in pain or function that was >=20 mm on a 100 mm VAS, or a >=20% improvement in at least two of pain, function, or patient global assessment that was >=10 mm on a 100 mm VAS).[38]

"Harms" include tolerability (not having to stop the drug due to adverse effects); cardiovascular, hepato-, renal, and gastrointestinal toxicity; and increased risk for hospitalizations, drug interactions, and death. For gastrointestinal toxicity, we focused on serious complications associated with NSAIDs including perforation, bleeding ulcer, and gastric

outlet obstruction, though we also evaluated other gastrointestinal side effects (such as nausea, dyspepsia, and gastrointestinal tolerability. We only considered rates of endoscopic ulcers when data on clinical ulcer complications were incomplete or not available.

2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?

- Demographic subgroups include age, sex, and race.
- Co-existing diseases include hypertension, edema, ischemic heart disease, heart failure, PUD, and history of previous bleeding due to NSAIDS.
- Concomitant medication use includes anticoagulants and aspirin.

3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors?

4. What are the benefits and safety of treating osteoarthritis with oral medications as compared with topical preparations?

Topical preparations include:

- Capsaicin
- Diclofenac
- Ibuprofen
- Ketoprofen
- other NSAIDs
- salicylates

Chapter 2. Methods

Topic Development

The topic for this report was nominated in a public process. The key questions were developed by investigators from the Oregon EPC with input from a Technical Expert Panel (TEP) formed for this project. Contacted via teleconference, the TEP served in an advisory capacity for this report, helping to refine key questions, identify important issues, and define parameters for the review of evidence.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. Results from previously conducted meta-analyses and systematic reviews on these topics were sought and used where appropriate and updated when necessary. To identify systematic reviews, in addition to MEDLINE, we searched the Cochrane Database of Systematic Reviews and the websites of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Bandolier, and the NHA Health Technology Assessment Programme.

To identify articles relevant to each key question, we searched the Cochrane Database of Systematic Reviews (through 3rd Quarter 2005) the Cochrane Central Register of Controlled Trials (through 3rd Quarter 2005) and Ovid ®MEDLINE (1966- July, 2005.) We used relatively broad searches, combining terms for drug names with terms for relevant research designs, limiting to those studies that focused on osteoarthritis and rheumatoid arthritis (see Appendix D for the complete search strategy). Other sources include reference lists of review articles and unpublished materials from the US Food and Drug Administration (FDA). Pharmaceutical manufacturers were invited to submit scientific information packets, including citations if applicable. All 2,665 citations from these sources were imported into an electronic database (EndNote® 9.0) and considered for inclusion.

Study Selection

Systematic reviews and controlled trials pertinent to the key questions were included. We retrieved any blinded or open, parallel or crossover randomized controlled trial that compared one included drug to another, another active comparator, or placebo. We also included cohort and case-control studies with at least 1,000 cases or participants that evaluated serious gastrointestinal and cardiovascular endpoints that were inadequately addressed by randomized controlled trials.

Data Extraction

The following data were extracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), method of outcome ascertainment if available, and results for each outcome, focusing on efficacy and safety. We recorded intention-to-treat results if available.

Quality Assessment

Assessing Research Quality

We assessed the internal validity (quality) of systematic reviews and randomized trials based on the predefined criteria listed in Appendix E. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[39] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix E) assessing whether they had a clear statement of the questions(s), reported inclusion criteria, used an adequate search strategy, assessed validity, reported adequate detail of included studies, and used appropriate methods to synthesize the evidence. We included systematic reviews and meta-analyses that included unpublished data inaccessible to the public, but because the results of such analyses are not verifiable, we considered this a methodological shortcoming.

For assessing the internal validity of observational studies, we evaluated whether they used nonbiased selection methods; whether rates of loss to follow-up were acceptable; whether pre-defined outcomes were specified; whether they used appropriate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders. Although many tools exist for quality assessment of nonrandomized trials, there is no consensus on optimal quality rating methods.[40] We therefore did not use a formal scoring system to rate the quality of the observational studies included in this review, but noted methodological deficiencies in any of the above areas when present.

Assessing Research Applicability

The applicability of trials and other studies was assessed based on whether the publication

adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, whether differences in outcomes were clinically (as well as statistically) significant, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the sponsor.

Rating a Body of Evidence

Overall quality ratings for an individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

We assessed the overall strength of evidence for a body of literature about a particular key question, by examining the type, number and quality of studies; the strength of association; the consistency of results within and between study designs; and the possibility for publication bias. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered "good-quality.") For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm.

Data Synthesis

Effectiveness Versus Efficacy

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes of most importance to patients, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the "average" patient than results from highly selected populations in efficacy studies. Examples of "effectiveness" outcomes include quality of life, global measures of successful treatment, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales. Further discussion of these issues is available at http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

Data Presentation

We constructed evidence tables showing study characteristics, quality ratings, and results for all included studies. We also performed two quantitative analyses for this review. An important limitation of observational studies of NSAIDs is that none simultaneously assessed the risk for

serious cardiac and GI events. We therefore re-analyzed data from a set of observational studies that reported rates of three different serious adverse events in the same population. We assumed that the adverse events occurred independently and that the logarithm of the rate ratios was distributed normally. After estimating the effect (number of events prevented or caused) for each of the three adverse events, we estimated the net effects on all three serious adverse events using Monte Carlo simulation.

We also pooled clinical success rates and withdrawal due to adverse events from head-to-head trials of topical versus oral NSAIDs using a random effects model (Dersimonian-Laird method, using RevMan® statistical software). We performed standard chi-square tests for heterogeneity. Because only four trials were available for pooling, we did not attempt meta-regression analyses to evaluate potential sources of heterogeneity.

Chapter 3. Results

Overview

Searches identified 2,789 publications: 1,522 from the Cochrane Central Register of Controlled Trials, 68 from the Cochrane Database of Systematic Reviews, 1015 from MEDLINE and 184 from the combination of other sources listed above. There were also 59 studies not previously reviewed for inclusion that were suggested through peer review or public comment or published after the searches were conducted. Following application of inclusion criteria, 351 publications were included in this review.

Key Question 1a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?

Benefits: Effectiveness and Efficacy

Effectiveness Studies

No controlled clinical trials of COX-2 inhibitors and/or NSAIDs met all major criteria for an effectiveness study (conducted in mainly primary care or office-based settings, used broad enrollment criteria, and evaluated longer-term, "real-life" outcomes).

Efficacy

Non-selective NSAIDs vs. other NSAIDs. Several good-quality systematic reviews by the Cochrane Collaboration evaluated trials that compared non-aspirin NSAIDs for OA of the hip (trials published through 1994),[41] for OA of the back (through 1998),[10] and for OA of the knee (through 1997).[42] These reviews found no clear differences among non-aspirin and primarily non-selective NSAIDs in efficacy. There were also no differences between diclofenac and sustained-release etodolac in patients with OA of the knee[43] or between piroxicam and standard formulation etodolac in patients with OA of the knee or hip[44] in two trials published subsequent to the Cochrane reviews.

Nabumetone was similar in efficacy to the non-selective NSAIDs diclofenac SR[45] and etodolac[46] in two 4-week trials, as reported in the Cochrane review of OA of the knee.[42]

No studies of meloxicam, salsalate, or aspirin were included in any Cochrane reviews. We identified nine double-blinded trials of meloxicam 7.5 mg, 15 mg, and 25 mg versus other NSAIDs and found no clear or consistent differences in efficacy.[47-55] In two of the trials, however, patients taking non-selective NSAIDs were significantly less likely to withdraw due to

lack of efficacy than patients taking meloxicam. [49, 54]

In the only head-to-head trial of salsalate (3 g) in patients with OA, efficacy was similar to that of 3.6 g soluble aspirin after two weeks of treatment.[56]

Celecoxib vs. non-selective NSAIDS. Celecoxib and non-selective NSAIDs were associated with similar decreases in symptom severity and improvements in functional capacity (PGA, WOMAC) after 6- to 24-weeks in five published trials of patients with primarily OA. [57-60]

A good-quality systematic review funded by the makers of celecoxib reached similar conclusions based on data from published and unpublished trials of at least 12 weeks' duration in patients with either OA or RA.[61]

Using an alternative endpoint, a more recent systematic review (published in 2005) with access to all unpublished manufacturer-held clinical trial reports reached slightly different conclusions about the relative efficacy of celecoxib and NSAIDs.[62] Moore et al meta-analyzed data from 31 primarily short-term (≤ 12 weeks) trials and concluded that celecoxib at dose of 200-400 mg was associated with slightly higher rates of withdrawals due to lack of efficacy compared to non-selective NSAIDs (RR 1.1; 95% CI 1.02, 1.23). CLASS remains the pivotal, long-term study (6 to 13 months) of celecoxib in patients with rheumatoid and osteoarthritis. It randomized a total of 7,968 patients to celecoxib or the non-selective NSAIDs ibuprofen or diclofenac. A higher proportion of non-selective NSAID patients withdrew due to lack of efficacy (14.8% vs. 12.6%, p=0.005). However, CLASS focused on assessment of adverse events rather than efficacy, and other efficacy results were reported. SUCCESS-1, a shorter (12-week), double-blind, randomized trial of 13,274 patients with osteoarthritis, found no clinically meaningful differences between celecoxib 100 mg or 200 mg twice daily and the non-selective NSAIDs diclofenac or naproxen.[63]

Rofecoxib vs. non-selective NSAIDs. We were unable to determine whether all manufacturer-sponsored trials of rofecoxib versus NSAIDs have been published.[19, 64-76] All but one of the trials included osteoarthritis patients, and all but two[70, 72] were supported by the manufacturer of rofecoxib. All but two of the OA trials[73, 76] have been previously analyzed in a good-quality Cochrane review.[77] Conclusions of the Cochrane review are consistent with our findings that there were no consistent differences between rofecoxib and non-selective NSAIDs in efficacy for OA. In addition, a pivotal, good-quality trial (VIGOR) and a good-quality Cochrane review found rofecoxib equivalent to naproxen in efficacy for rheumatoid arthritis.[19, 78]

Valdecoxib vs. non-selective NSAIDs. In clinical trials submitted to the FDA, valdecoxib was as effective as ibuprofen (800 mg 3 times/day), diclofenac (75 mg twice daily), and naproxen (500 mg twice daily) in treating osteoarthritis symptoms. Published trials found no difference in efficacy between valdecoxib and naproxen[79-81] or ibuprofen or diclofenac.[82] A fifth trial found no difference in efficacy between valdecoxib 20-40 mg and slow-release diclofenac 75 mg in treating rheumatoid arthritis.[83]

Comparisons between selective COX-2 inhibitors. We found six published randomized, multicenter, fair-to-good quality trials that directly compared COX-2 inhibitors for osteoarthritis of the knee.[84-89] Pharmaceutical manufacturers were reported as funding sources in all but one study.[88] This small (N=30), short-term (7 days), fair-quality trial found that rofecoxib 25 mg and celecoxib 200 mg had similar effects on patients' pain intensity, 3-hour pain relief, global

assessment of efficacy and rescue medication use.[88] Two trials of higher-risk osteoarthritic patients with hypertension (both funded by the maker of celecoxib) found no differences in efficacy between rofecoxib 25 mg and celecoxib 200 mg daily, but reported a higher rate of adverse events with rofecoxib.[84, 85]

The remaining three trials appeared to enroll patients with similar demographics and baseline levels of pain and were more homogeneous in design (see table below).[86, 87, 89] All compared rofecoxib 25 mg qd and celecoxib 200 mg qd in patients with flare-ups of chronic osteoarthritis of the knee and were 6 weeks in duration. One trial, funded by the manufacturer of celecoxib, found no difference in efficacy between rofecoxib and celecoxib, but a higher rate of adverse events with rofecoxib.[86] Another (VACT, or *Vioxx Acetaminophen Celecoxib Trial*)[87] trial, funded by the manufacturer of rofecoxib, found rofecoxib more effective than celecoxib, with no differences in rates of adverse effects. The most recent study, funded by the maker of celecoxib,[89] found no difference in either efficacy or adverse effects between celecoxib and rofecoxib.

Table 2. Comparison of rofecoxib and celecoxib in flare-ups of chronic osteoarthritis of the knee

Characteristic	McKenna[86]	Geba[87]	Gibofsky[89]
Rofecoxib 25mg (n)	59	95	190
Celecoxib 200mg (n)	60	97	189
Aspirin 325 qd permitted	Yes	No	Yes
Mean age	62	62.6	62.9
Mean osteoarthritis duration	10.5 years	10 years	9 years
Percent white	80%	85%	NR
Baseline pain on walking (score)	72	72	68
Discontinued trial by 6 wks:			
Rofecoxib 25mg	16%	19%	15%
Celecoxib 200mg	22%	17%	16%

All three trials were probably adequately randomized and blinded, and didn't have statistically significant differences in baseline characteristics. Gibofsky and colleagues hypothesized that neither McKenna nor Geba were powered sufficiently to measure differences between celecoxib and rofecoxib. Gibofsky viewed the McKenna study as being powered only to compare active treatments with placebo and the Geba study as powered to compare rofecoxib with acetaminophen. Therefore, Gibofsky, and colleagues set out to conduct a study powered to compare celecoxib and rofecoxib, with a sample size based on results of the McKenna study.

Efficacy results are summarized in Table 3 below. Mean changes in WOMAC VAS score for Walking Pain were similar for celecoxib 200 mg and rofecoxib 25 mg across trials. In the Geba trial, rofecoxib was associated with significantly greater mean reductions than celecoxib on VAS scores for WOMAC Rest Pain and Night Pain and a similar mean reduction in Morning Stiffness. WOMAC Composite Score results from Geba and Gibofsky were conflicting. In the Gibofsky trial, there were no differences, but in the Geba trial, there were significant differences favoring rofecoxib for mean changes in the WOMAC pain (7 points) and stiffness (8 points) subscales. However, an analysis of data from randomized trials estimated that the minimal perceptible improvement for each WOMAC scale was a difference of 11 mm.[90]

Table 3. Head to head efficacy comparisons at 6 weeks (mean change from baseline)

	WOMAC VAS Scores					*WOMAC Composite Subscales*			
	Walking pain	Rest pain	Morning stiffness	Night pain	Arthritis pain	Pain	Stiffness	Function	Total
Geba[87]									
Rofecoxib	-42	-31.1*	-36.2	-32.7**	nr	-35.4*	-35*	-29.7	-26
Celecoxib	-36.2	-23.4	-29.1	-22.6	nr	-28.6	-27.9	-24.9	-26
McKenna[86]									
Rofecoxib	-38	nr	nr	nr	-40	nr	nr	nr	nr
Celecoxib	-38	nr	nr	nr	-39	nr	nr	nr	nr
Gibofsky[89]									
Rofecoxib	-29.2	nr	nr	nr	nr	-42.6	-34.7	-35.5	-20.1
Celecoxib	-31.5	nr	nr	nr	nr	-42.0	-36.7	-37.9	-22.1

*p≤0.05; **p<0.001; nr=not reported

Safety: Serious Gastrointestinal and Cardiovascular Events

Rofecoxib and Celecoxib: GI and CV Safety in CLASS and VIGOR

GI Safety

Two pivotal studies were large enough to evaluate serious complications of peptic ulcer disease (bleeding, perforations, obstruction) as a primary endpoint in average-risk patients (those without a recent UGI bleed). The VIGOR trial[19] evaluated rofecoxib versus naproxen and the CLASS trials[60] evaluated celecoxib versus ibuprofen and diclofenac.

VIGOR (Vioxx Gastrointestinal Outcomes Research) Trial. VIGOR, a randomized, double-blind trial, compared twice the highest recommended dose of rofecoxib (50 mg daily) to naproxen 500 mg twice a day in 8,076 patients with rheumatoid arthritis. VIGOR found a statistically significant reduction in complicated upper GI events (defined as perforation, obstruction, or severe upper gastrointestinal bleeding. During a median follow-up of 9 months, the rates of confirmed upper gastrointestinal events were 3.0% vs. 1.4% (NNT to prevent one event 62), and the rates of complicated, confirmed upper gastrointestinal events were 0.9% vs. 0.4% (NNT 192).

VIGOR met all but one of the criteria for a good-quality study. The one weakness was the varying duration of exposure among study participants. The duration of VIGOR was designed to be both time and event driven, so that the trial would terminate after a minimum of 120 patients experienced clinical upper GI events (or 40 patients experienced complicated upper GI events) and for at least 6 months after randomization of the last patient enrolled. Because patients were enrolled over a 6-month period, patients in VIGOR were followed for varying lengths of time. The longest time a patient could have remained in the study was 13 months, but half of the patients were followed for 9 months or less, and only about 1,000 patients (13%) were followed for longer than 10 months. By 13 months, about 29% of the subjects had discontinued the study drugs. Similar proportions discontinued naproxen or rofecoxib because of an adverse event (naproxen—16.1%, rofecoxib—16.4%).

In 2003, the VIGOR investigators published a *post hoc* analysis of lower GI events, defined

as bleeding with a 2 g/dL drop in hemoglobin or hospitalization, or hospitalization for perforation, ulceration, diverticulitis, or obstruction.[91] There were 11 events in the rofecoxib group and 24 events in the naproxen group (0.41 versus 0.89 per 100 patient-years; RR 0.46, 95% CI 0.22 to 0.93). The absolute risk difference (per 100 patient-years) was –0.48 (95% CI – 0.91 to –0.05), with a NNT of 208. When the investigators combined the analysis of lower GI events with previously reported results on upper GI complications (0.6 with rofecoxib versus 1.4 with naproxen per 100 patient-years[92]), the rates of all serious GI events were 0.96 for rofecoxib and 2.26 per 100 patient-years for naproxen (relative risk 0.43, 95% CI 0.27 to 0.67, NNT 77).

CLASS (Celecoxib Long-term Arthritis Safety Study.) CLASS was designed as two trials with separate patient recruitment and randomization procedures: one compared celecoxib 400 mg twice a day with ibuprofen 800 mg three times a day, and the other compared celecoxib 400 mg twice a day with diclofenac 75 mg twice a day.[60] Because the FDA was concerned that selective COX-2 inhibitors could interfere with the benefits of COX-2 in ulcer healing and lead to a long term increase in GI complications without warning symptoms, the pre-specified primary outcome was "ulcer-related complications."[93] Another pre-specified outcome was ulcer related complications plus symptomatic ulcers. The planned maximum duration of the trials were 15 and 12 months, respectively, or until at least 20 ulcer-related complications occurred in each trial, or 45 in both trials combined.[94] The protocols stated that celecoxib would be claimed to be different from traditional NSAIDs only if there were statistically significant differences between celecoxib and each of the comparators, as well as between celecoxib versus the comparator groups combined.

The CLASS trials were stopped early after the predefined threshold of ulcer complications occurred. However, the analysis and reporting of the results as presented in the main publication in JAMA were in part incomplete and differed in some ways from the protocols. The JAMA article reported truncated 6-month results even though the median duration of follow-up was 9 months (range 6 to 13 months), and combined the ibuprofen and diclofenac results without reporting the results of the two trials separately.[60] Subsequently, additional details of the study have been made public on the FDA web site[94] and have been extensively analyzed. The findings of the FDA analysis suggest that the published results of CLASS are, in part, misleading because they appear to selectively report results at the point in time at which celecoxib was most effective.[95-97]

There were 3,987 subjects randomized to celecoxib and 3,981 subjects randomized to non-selective NSAIDs in the CLASS trials. For the combined outcome of ulcer complications or symptomatic ulcers, the JAMA article reported that patients on celecoxib experienced fewer GI complications compared with patients in the combined NSAID groups (32/3987 versus 51/3981, annualized incidence rates 2.08% vs. 3.54%, p=0.02),[60] while the rate of complicated ulcers alone was not significantly different (13/3987 vs. 22/3981, annualized incidence rates 0.76% vs. 1.45%, p=0.09). However, by 12 months, according to FDA documents (see Table 14, FDA Medical Officer Review)[94] there was no longer a trend favoring celecoxib for the primary outcome of complicated ulcers. There were 17/3987 events in the celecoxib group (0.43%) versus 21/3981 (0.53%) in the NSAID groups combined.[94] This difference was not statistically significant (relative risk 1.10, 95% CI 0.47 to 2.58[97, 98], also see Figure 4, Scheiman review[99]). For the individual comparisons between celecoxib and ibuprofen or diclofenac, which were not reported in the JAMA article, there was no difference in the rate of ulcer complications at either 6 months or at the end of follow-up.[97] For the outcome of ulcer complications or symptomatic ulcers, celecoxib was superior to ibuprofen, but not to diclofenac at either 6 months or at the end

of follow-up.[97]

Authors of CLASS have not completely explained the reasons for selective reporting of results, though they contend that combining the two trials and reporting ulcer complications plus symptomatic ulcers as a primary outcome were permitted by the protocols.[100, 101] However, reporting only combined results appears to obscure differences between the results for the two comparator drugs.[96] The investigators' main argument for reporting truncated data is that results after 6 months were not interpretable because of high and differential rates of drop-outs due to symptomatic ulcers, which could have biased results against celecoxib because of depletion of high-risk patients in the non-selective NSAID arms.[100, 101] On closer inspection, however, this rationale appears flawed, as neither symptomatic ulcers nor gastrointestinal symptoms predicted ulcer complications.[96] Furthermore, simply truncating data is not considered an acceptable method for resolving issues related to high drop-out rates.

Twenty per cent of the patients in the CLASS trial took aspirin in addition to their study. drug. When patients taking aspirin were excluded from the analysis, there were fewer confirmed serious ulcer complications in the celecoxib group than in the ibuprofen group ($p=0.03$).[94, 97] However, serious ulcer complications for celecoxib and diclofenac were equivalent even when patients taking aspirin were excluded from the analysis.

Changes in hemoglobin or hematocrit were not a primary outcome of CLASS and were not reported in the main JAMA publication. However, rates of significant hemoglobin (>2 g/dL) and/or hematocrit drops (>=0.10), a surrogate marker for GI blood loss, are available from the FDA Medical Officer Review.[94] Over the entire study period, patients randomized to celecoxib were significantly less likely to experience declines in these laboratory parameters (87/3701 or 2.4%) relative to patients randomized to either diclofenac (82/1849 or 4.4%) or ibuprofen (102/1802, 5.7%). Celecoxib was also superior when patients were stratified according to aspirin use (4.1% vs. 6.9% and 7.5%) or non-use (1.9% vs. 3.7% and 5.2%). However, the significance of these findings is unclear as they were not associated with differences in clinically relevant outcomes (such as rates of MI, angina, or congestive heart failure).

In summary, the CLASS trials did not demonstrate a statistically significant advantage over either diclofenac or ibuprofen for the primary endpoint of complicated ulcers for all patients enrolled over the full duration of follow-up. Celecoxib appeared superior to ibuprofen, but not diclofenac, in a subgroup of subjects not taking aspirin. In its decision regarding labeling for celecoxib, the FDA agreed with its Advisory Committee recommendations that CLASS did not demonstrate a safety advantage in upper gastrointestinal safety for celecoxib compared with either ibuprofen or diclofenac.[102]

Comparison between VIGOR and CLASS. There are several possible reasons why rofecoxib (VIGOR), but not celecoxib (CLASS), significantly reduced ulcer complications. First, patient populations and study designs differed. VIGOR included patients aged 50 or older with rheumatoid arthritis, while CLASS had a broader age range of patients with either osteoarthritis or rheumatoid arthritis. VIGOR also prohibited the use of aspirin while CLASS did not. However, the rate of ulcers in the patients taking a control drug was almost three times as high in VIGOR as in CLASS, although rates of ulcer complications were similar. In addition, VIGOR compared rofecoxib to naproxen and CLASS compared celecoxib to diclofenac and ibuprofen. This could have affected the results if the non-selective comparator NSAIDs are associated with differential risk of ulcers. Finally, it is possible that rofecoxib, which has greater COX-2 selectivity, is truly more gastroprotective than celecoxib.

CV Safety

CV risk in VIGOR. Findings from the VIGOR trial raised concerns that the putative GI safety benefits of COX-2 selective NSAIDs relative to non-selective NSAIDs may have come at the expense of increased cardiovascular events. The main publication of VIGOR[19] reported that "the incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups." This corresponds to one additional heart attack for every 333 patients treated with rofecoxib instead of with naproxen. A re-analysis of VIGOR with three additional myocardial infarctions not included in the results originally submitted for journal publication estimated a relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen among all patients, and 3.00 (95% CI 0.91 to 12.78) among patients in whom aspirin was not indicated.[103] For patients who had indications for aspirin, 8 MIs occurred during 105 person-years of exposure to rofecoxib, compared with no MIs during 102 person-years of exposure to naproxen. Blinded adjudication of the VIGOR trial data classified 45/4047 (one in every 90) rofecoxib patients and 19/4029 (one in 212) naproxen patients as having serious thrombotic events (heart attack, stroke, unstable angina, transient ischemic attack, resuscitated cardiac arrest, and sudden death).[104] This corresponds to one additional serious thrombotic event for every 156 patients taking rofecoxib.

CV risk in CLASS. The original publication of the CLASS trials, using 6-month data, reported that celecoxib had no effect on the rate of myocardial infarction or for any cardiovascular event (stroke, myocardial infarction, or angina) compared with diclofenac and ibuprofen.[60] The number of myocardial infarctions was 10/3987 (0.3%) with celecoxib versus 11/3981 (0.3%) with the non-selective NSAIDS). The full CLASS data on thrombotic events were analyzed in more detail by White and colleagues,[105] who also found no differences in the rates of any significant cardiovascular event for the overall sample or for the subgroup who did not use aspirin. For the overall sample, myocardial infarctions occurred in 19/3987 (0.5%) of patients on celecoxib and 13 (0.3%) on diclofenac or ibuprofen. In fact, more detail about the design of the CLASS trials is necessary to judge the validity and generalizability of these results. In particular, reporting of longer-term data is important because 6 months of exposure to celecoxib may not be enough time to assess cardiovascular risk. At 8 months in the VIGOR trial there was no significant difference between rofecoxib and naproxen in the cumulative incidence of events. From 8 to 12 months, differences in the incidence of myocardial infarction between rofecoxib and naproxen became apparent (Figure 1 of Mukherjee[106]). This observation could be due to increased power due to a larger number of events with longer follow-up, or in part to a duration-dependent increase in risk. Based on the pattern observed in VIGOR, if celecoxib is associated with an increased risk of cardiovascular events, it may not be seen until 10 or 12 months of followup. In the VIGOR trial, 2,140 subjects, about one-fourth of the original sample, were available for 10 months of followup, and 1,045 were available for 12 months. In the CLASS trials, 2,770 subjects, about one-third of the original sample, had at least 9 months of follow-up, and 1,126 had at least 12 months of follow-up, suggesting that an analysis should have been able to detect an increased risk of cardiovascular events similar to that observed in VIGOR, if it was present (see Table 4, FDA Medical Officer Review[94]).

White and colleagues argue that their meta-analysis shows that celecoxib is safer than rofecoxib.[105] To support their argument, they note that the annualized rate of all cardiovascular

thromboembolic events in the naproxen group in the VIGOR trial and the non-aspirin celecoxib users in the CLASS trial were similar. However, this comparison of rates across the VIGOR and CLASS studies is imprecise. After 8 months, about 0.4% of naproxen patients had experienced an event in VIGOR, compared to about 0.8% of non-aspirin celecoxib users in CLASS. It is not clear whether or not this is a statistically significant difference. By contrast, Mukherjee and colleagues suggested that the selective NSAIDs as a class might be associated with an increased risk of myocardial infarction because the 0.8% rate of myocardial infarction on celecoxib in the CLASS trials and the 0.74% rate on rofecoxib in VIGOR are both higher than the 0.52% rate observed in a meta-analysis [107] of patients receiving placebo in studies of aspirin prophylaxis.[106] In our opinion, all of these conclusions are unsubstantiated because they involve cross-trial and historical comparisons.

The importance of analyzing longer-term data and assessing dose effects are underscored by the results of the long-term Adenoma Prevention with Celecoxib (APC) trial in a different population—that of patients receiving celecoxib for colorectal polyp prevention.[108] This trial, which randomized patients to celecoxib versus placebo, was terminated after 33 months because of a higher rate of cardiovascular events (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) in the celecoxib arms. According to Figure 1 in the main publication of this trial,[108] the difference in rates of events became most apparent only after twelve to eighteen months. There was also a non-significant increase in risk with higher compared to lower doses of celecoxib. Compared with placebo, the relative risk of cardiovascular events in patients randomized to celecoxib 400 mg twice daily was 3.4 (95% CI 1.4 to 8.3) compared to 2.5 (95% CI 1.0 to 6.3) in patients randomized to 200 mg twice daily.[108] Much of the increased risk was due to differences in rates of fatal or nonfatal myocardial infarctions, which occurred in 22/1356 (1.6%) of celecoxib users and 3/679 (0.4%) of patients on placebo.[109] On the other hand, data from PreSAP,[110] another polyp prevention trial, and preliminary data from ADAPT,[111] an Alzheimer's prevention trial, found no significant increase in cardiovascular events with celecoxib 400 mg once daily (PreSAP, RR 1.3, 95% CI 0.6 to 2.6[109]) or 200 mg twice daily (ADAPT) compared to placebo. However, the lack of an association could be due to insufficient power to detect a difference because of the small number of myocardial infarctions associated with celecoxib in these trials (2 in ADAPT[112] and 9 in PreSAP[109]). Alternatively, the smaller relative risk in PreSAP relative to APC could be related to a higher placebo event rate in PreSAP (7.2 versus 3.4 per 1000 patient-years).[109] SUCCESS-I, a recently published, large (N=13,274) trial of osteoarthritis patients, also reported no significant difference in rates of cardiovascular thromboembolic events with celecoxib 100 mg or 200 mg twice daily versus diclofenac or naproxen (10 events or 0.55/100 patient-years in the combined celecoxib arms versus 1 event or 0.11/100 patient-years in the non-selective NSAID arms, p=0.11), but may have been too short in duration (12 weeks) and have recorded too few events to detect a difference.[63]

Overall rate of serious adverse events in CLASS and VIGOR. One Canadian analysis used FDA materials to analyze the rates of serious adverse events, defined as death, hospitalization, or "any life-threatening event, or event leading to severe disability" in the CLASS and VIGOR trials.[113] This measure combines the rates of serious upper GI complications (in which coxibs are expected to have an advantage over NSAIDs) with other serious adverse events. The numbers of all serious adverse events were drawn directly from FDA materials, pages 7 and 8 (rofecoxib[114]) and 57 (celecoxib[94]).

In the Canadian re-analysis, shown in Table 4, the rates were calculated using the number of patients as the denominator. These simple rates are compared with the number of serious upper GI events, which constitute only about 10% of all serious adverse events (the two rightmost columns in the table). Using all serious adverse events as the criterion for "harm," the number-needed-to-harm one person was 82 for celecoxib vs. diclofenac, 129 for celecoxib vs. ibuprofen, 100 for celecoxib vs. diclofenac and ibuprofen, and 65 for rofecoxib vs. naproxen. The Canadian authors also pooled the results for celecoxib and rofecoxib, assigning more weight to VIGOR, which had a longer duration than CLASS. In the pooled analysis, the number needed to harm was 78 for the selective COX-2 inhibitors versus non-selective NSAIDs and was statistically significant.

Table 4. Re-analysis of the CLASS and VIGOR Trials[113]

	ALL SERIOUS ADVERSE EVENTS		SERIOUS UPPER GI EVENTS	
Trial	Treatment	Control	Treatment	Control
CLASS[60] (Celecoxib 400 mg)	270/3987 (6.8%)	230/3981(5.8%)	20/3987 (0.5%)	24/3981 (0.6%)
VIGOR [19] (Rofecoxib 50 mg)	378/4047 (9.3%)*	315/4029 (7.8%)	16/4047 (0.4%)*	37/4029 (0.9%)

*statistically significant vs. control group.

For the VIGOR trial, the FDA calculated rates of serious adverse events in exactly the same manner as the Canadian investigators.[114] The FDA analysis shows that the rates of each serious adverse event (except GI adverse events) were higher for rofecoxib than for naproxen. For the CLASS trials, the FDA used patient-years as the denominator instead of a simple proportion to calculate rates of serious adverse events.[94] This approach was used because the two trials that make up CLASS had different durations. In the FDA analysis, the rates of all serious adverse events combined were 11.6 per 100 patient-years for celecoxib; 10.3 per 100 patient-years for diclofenac, and 10.6 per 100 patient-years for ibuprofen, a difference that was not statistically significant.

In summary, the FDA data clearly show that these two coxibs, in doses higher than those commonly used in practice, do not reduce the overall rate of serious adverse events, and may have increased them. It should be noted, however, that not all serious adverse events are equal in importance to patients and physicians. A reduction in the rate of one kind of adverse event might be considered more important than an increase in another one.

Rofecoxib and Celecoxib: Further Analyses of CV Toxicity and GI Safety

The GI and CV risk profiles of celecoxib and rofecoxib relative to one another and to NSAIDs, placebo, or no treatment have also been assessed in numerous meta-analyses of randomized trials and observational studies. We were unable obtain final results of one systematic review evaluating the GI safety associated with selective and non-selective NSAIDs in time to include it in this report.[115] However, analyses of GI safety with celecoxib and rofecoxib in this systeamtic review were based on results from CLASS,[60] VIGOR,[19] the then-unpublished SUCCESS-1 trial of celecoxib,[116] and two previously published meta-analyses[117, 118] (all included in this report).

Rofecoxib. VIGOR remains the only individual trial large enough to adequately assess rates of upper GI complications with rofecoxib and non-selective NSAIDs in patients with arthritis. However, the manufacturer of rofecoxib also sponsored a prospective meta-analysis of GI safety from eight smaller phase 2b/3 osteoarthritis trials (N=5425).[118] It found the 12-month combined incidence of perforations, symptomatic ulcers, and upper GI bleeding significantly lower with rofecoxib compared to non-selective NSAIDs (1.3% vs. 1.8%, P=0.046; rate per 100 patient-years 1.33 vs. 2.60, RR 0.51, 95% CI 0.26 to 1.00). The rate of ulcer complications alone, however, was not reported. A Food and Drug administration review has been critical of several aspects of this meta-analysis.[119] It notes that it is not clear how assiduously investigators of the trials adhered to the pre-specified protocols (for example, by not delivering the prespecified type of primary source material mandated in the original protocol), and that most (50 of 62) cases were unblinded before the adjudication process occurred. In addition, the FDA review suggests that simple pooling and comparisons of the rofecoxib and the non-selective NSAIDs outcomes may be misleading because study duration varied, different patient withdrawal criteria were applied, different diagnostic surveillance methods (including endoscopic surveillance in two trials) were employed, doses of rofecoxib varied, and different comparator NSAIDs were used. Rates of complicated ulcers at 12 weeks, for example, were substantially higher in patients on ibuprofen (1.12%) compared with diclofenac (0.19%). Further, combining symptomatic ulcers and ulcer complications may be less informative because the morbidity associated with ulcer complications is substantially higher than the morbidity associated with symptomatic ulcers. Data reported on the FDA web site (page 78) indicate that only six complicated ulcers in 3,357 patients on rofecoxib and five in 1,564 patients on non-selective NSAIDs (cumulative incidence at 12 months 0.45% vs. 0.55%) occurred; the difference was not statistically significant (relative risk using Cox proportional hazards model 0.51, 95% CI 0.16 to 1.69).[119]

An updated meta-analysis of 20 trials sponsored by the manufacturer of rofecoxib (excluding VIGOR) reported 0.21 vs. 0.45 confirmed complicated PUBs per 100 patient-years of exposure (p=0.03) among 10,026 subjects randomized to rofecoxib and 7,046 to non-selective NSAIDs. However, this meta-analysis was rated fair-quality because it did not evaluate the effects of study quality, duration of therapy, or dose (about 30% of patients received 12.5 mg of rofecoxib, about 50% received 25 mg, and about 10% received 50 mg).[120] With regard to duration of exposure, the results as presented in this study are somewhat misleading, as the rate of PUBs are reported as occurring over 24.8 months (last point in time at which there were >200 patients left in each treatment group), even though the median duration of exposure was only 3 months. Only one-quarter of the patients receiving rofecoxib had over 6 months of exposure.

The only randomized controlled trial evidence clearly demonstrating a lower risk of complicated ulcers with long-term use of rofecoxib compared with non-selective NSAIDs therefore comes from VIGOR, which evaluated a higher-than-conventional dose of 50 mg of rofecoxib. Although the most recent meta-analysis[120] reporting rates of complicated ulcers is consistent with VIGOR, its results appear primarily applicable to patients with shorter-term (<6 months) exposure to rofecoxib.

Celecoxib. One manufacturer-funded, fair-quality meta-analysis examined the endpoint of "UGI ulcer complications" in 14 RCTs of celecoxib (not including CLASS) versus placebo or non-selective NSAIDs (usually naproxen).[121] The trials ranged in duration from 2 to 24 weeks, with most lasting 6 or 12 weeks. The strength of this meta-analysis was that the endpoint—upper

GI bleeding with endoscopic findings of an ulcer or large erosion, perforation, or gastric outlet obstruction—was similar to those used in the VIGOR and CLASS trials. A Safety Committee adjudicated potential ulcer complications in a blinded manner. These endpoints were ascertained through a monitoring program that appears to have been superimposed on all of the trials; it is not clear how assiduously investigators complied with this program. Not all of the included trials have been published, and their quality was not assessed as part of the meta-analysis. In addition, like the meta-analysis of rofecoxib trials described above, results of the trials were simply pooled despite differences in dose of celecoxib, duration of therapy, or which comparator NSAID was used. In the 14 trials, there were 2 UGI ulcer complications among 6,376 patients in the celecoxib group (3 per 10,000), 9 among 2,768 in the NSAIDs group (33 per 10,000) and none in the placebo group (0/1,864). This corresponded to annual rates of two per 1,000 per year for celecoxib and about 17 per 1,000 per year for NSAIDs (p=0.002).

There are several possible reasons why the results of the meta-analysis differed from those of CLASS, which did not clearly show a decreased risk of UGI ulcer complications for celecoxib compared to diclofenac and ibuprofen. First, the incidence of serious ulcer complications in CLASS was much higher than in the trials included in the meta-analysis. In the CLASS trials, the annualized rate of serious ulcer complications was 7.6 per 1,000 per year for celecoxib and 14.5 per 1,000 per year for the two NSAIDs combined.[60] The nearly four-fold higher rate of ulcer complications in the CLASS trials compared to the other celecoxib trials could be due in part to enrollment of a higher-risk population, the use of concomitant medications, the dose of celecoxib evaluated, or other factors. In CLASS, for example, 21% of patients randomized to celecoxib were on aspirin and 30.6% on corticosteroids. By contrast, only 12.4% of patients in the meta-analysis were taking aspirin, and 13.5% were on corticosteroids.[121] In addition, antiulcer medications (except for occasional antacids) were prohibited in CLASS, but used in 16.5% of celecoxib patients in the meta-analysis. Another potential explanatory factor is that the high dose of celecoxib used in CLASS—400 mg twice daily—was evaluated in only about 10% of the patients in the meta-analysis. It is possible that using higher doses of celecoxib could attenuate GI safety benefits because of incomplete COX-2 selectivity. Finally, different comparator NSAIDs could be associated with different risks of GI complications. In the meta-analysis, six trials (N=6151) compared celecoxib to naproxen versus only three trials (N=2439) that compared celecoxib to diclofenac or ibuprofen (the drugs evaluated in CLASS). Pooling data from trials evaluating different comparator NSAIDs could obscure differential effects on GI safety if they were present.

Moore, McQuay and others conducted a separate meta-analysis of celecoxib trials for osteoarthritis or rheumatoid arthritis, with funding from Pfizer and the Oxford Pain Relief Trust.[62] The authors obtained a declaration from Pfizer that they had received information on all completed clinical trials of celecoxib and would be permitted to publish the results no matter what their findings showed. However, much of the data on which this meta-analysis was based remains inaccessible to the public. The unpublished data used in this meta-analysis add value in that they may help provide the most comprehensive and precise estimates of adverse events. However, although the meta-analysis methods appeared appropriate, it is impossible to verify whether the meta-analysis assessed validity appropriately, abstracted outcomes correctly, or otherwise confirm the reproducibility of the meta-analysis.

Moore and colleagues reviewed over 180,000 pages of company documents, which included detailed information on study methods. All 31 included trials were rated 5 out of 5 on the Jadad quality scale, and 16 out of 16 on an eight-item validity scale. Only two of the 31 trials were

longer than 12 weeks in duration. The meta-analysis found celecoxib associated with a lower risk of hemoglobin fall of 20 g/L or more (a marker for a significant GI bleed) (RR 0.72, 95% CI 0.56 to 0.92) and hematocrit fall of 5% or more (RR 0.78, 95% CI 0.69 to 0.89) compared with non-selective NSAIDs.[62] Although the risk of complicated ulcers was not evaluated as a separate outcome, celecoxib was also associated with a lower risk of clinical ulcers and bleeds than non-selective NSAIDs in 18 trials (RR 0.61, 95% CI 0.46 to 0.81). When the analysis was limited to trials evaluating doses of 200 or 400 mg daily of celecoxib (in other words, excluding the results of CLASS), the benefit was more pronounced (RR 0.35, 95% CI 0.22 to 0.56).

The largest (N=13,274) randomized controlled trial (SUCCESS-1) of celecoxib (included in the Moore meta-analysis) assessed ulcer complications through 12 weeks.[63] It found that in patients with osteoarthritis, celecoxib was associated with a lower incidence of ulcer complications than naproxen or diclofenac (0.1% versus 0.8%, OR 7.02, 95% CI 1.46 to 33.8; p=0.008). Post hoc analysis indicated that non-aspirin users in the non-selective NSAID groups had a significantly higher risk of ulcer complications when compared to non-aspirin users in the celecoxib group (OR=12.05, 95% CI 1.45-100.09.) Among aspirin users, there was no statistically significant difference in the rates of ulcer complications for both NSAIDs and celecoxib.[63]

Systematic Reviews and Meta-analyses of CV Toxicity

Rofecoxib. VIGOR and other randomized trials of rofecoxib have been extensively re-examined to further explore its cardiovascular risk profile. Many questions have been raised in response to the disparate findings of these analyses and a myriad of possible explanatory factors have been proposed.

Rofecoxib versus non-selective NSAIDs. In October 2001, a fair-quality meta-analysis published in *Circulation*[122] by Konstam and colleagues reported pooled results from 23 rofecoxib Phase IIb through V trials sponsored by Merck. The investigators stratified results by patient group (rheumatoid arthritis, osteoarthritis, or Alzheimer's disease) and by control group (placebo, naproxen, or non-naproxen NSAID). The risk of cardiovascular events was 1.69 times higher for rofecoxib than for naproxen (95% CI 1.07 to 2.69), but was not elevated in trials comparing rofecoxib to non-naproxen NSAIDs (RR 0.79, 95% CI 0.40 to 1.55) (Table 5). The authors hypothesized that rofecoxib might have been an "innocent bystander" in the VIGOR trial. In other words, rather than rofecoxib increasing the rate of cardiovascular events, naproxen might have reduced it.

A problem with the Konstam analysis[122] is that the non-naproxen and naproxen studies are not directly comparable. VIGOR, the only long-term COX-2 trial to demonstrate a significant reduction in serious GI events, used rofecoxib 50 mg, prohibited aspirin, and followed patients for 9 months. By contrast, some of the non-naproxen-controlled studies were 12 weeks or shorter in duration, permitted aspirin, or used lower doses of rofecoxib. The data presented in the meta-analysis are also inadequate to judge the quality of the included studies and how concomitant aspirin use, duration of treatment, or dose might have affected rates of cardiovascular events, as adjustment using individual patient risk factors was not performed.

A subsequent meta-analysis by Reicen and colleagues, also rated fair-quality, provided a more detailed analysis of eight phase IIb/III trials of osteoarthritis patients previously included in the Konstam analysis.[123] Although the Konstam meta-analysis cites a planned duration of follow-up of 86 weeks for these trials, the Reicen meta-analysis reports that the mean duration of

treatment was actually 3½ months. Like the Konstam study, insufficient information was provided to judge the quality of the studies analyzed or the effects of concomitant aspirin. The incidence of thrombotic cardiovascular adverse events was lower in the rofecoxib treatment group (1.93/100 patient-years) compared with the non-naproxen NSAID (ibuprofen, diclofenac, or nabumetone) groups (2.27/100 patient-years) (Table 5).

The conclusion of the Reicen analysis—that there were no significant differences between rofecoxib and non-naproxen NSAIDs—may be valid for this set of studies. However, the results do not address the more specific question of whether rofecoxib is safe at the dosage proven to reduce serious GI events associated with long-term use. The analysis combined data from all rofecoxib doses (12.5, 25, and 50 mg/day); only 545 of the patients received the 50 mg/day dose. Although 50 mg/day is higher than doses used conventionally, the issue of dose may be important because only the 50 mg dose has been shown to reduce serious GI adverse events compared to non-selective NSAIDs in a long-term trial.[19] It is possible that lower doses of rofecoxib do not increase cardiovascular events compared with non-naproxen NSAIDs. However, even though lower, conventional doses of rofecoxib would be expected to be associated with lower long-term rates of GI ulcer complications compared to higher doses, this has not been proven in clinical trials.

Using a different methodology from the studies by Konstam and Reicen, a good-quality meta-analysis funded by the Swiss National Science Foundation came to different conclusions (Table 5).[124] Juni and colleagues included 18 randomized controlled trials of rofecoxib in patients with chronic musculoskeletal disorders (N=25,273), using published data on myocardial infarction as well as unpublished data available from the FDA. They found that the risk of myocardial infarction was higher in patients in the rofecoxib arms of trials compared with patients in the combined comparator arms (naproxen, non-naproxen NSAIDs, or placebo) (RR 2.24, 95% CI 1.24 to 4.02). The risk did not vary according to dose of rofecoxib or duration of therapy (shorter versus longer than 6 months). Trials with an external endpoint committee had a substantially higher risk for myocardial infarction (RR 3.88, 95% CI 1.88 to 8.02) than those without an external endpoint committee (RR 0.79, 95% CI 0.29 to 2.13). VIGOR contributed 8,076 of the 21, 432 included in the meta-analysis. However, even when the results of VIGOR were excluded, the increased risk of myocardial infarction in trials with an external endpoint committee persisted (RR 2.5, 95% CI 1.1 to 6.0).[125]

Table 5. CV events in trials of rofecoxib versus non-selective NSAIDs: meta-analyses

Study	Outcome	Comparison	Relative risk (95% CI)
Konstam, 2001[122]	Cardiovascular events	Rofecoxib versus non-naproxen NSAIDs Rofecoxib versus naproxen	0.79 (0.40-1.55) 1.69 (1.07-2.69)
Reicin, 2002[123]	Cardiovascular events	Rofecoxib versus non-selective NSAIDs	1.44 (0.65-3.17)
Juni, 2004[124]	Myocardial infarction	Rofecoxib versus any comparator Subgroup analyses: Rofecoxib versus non-naproxen NSAIDs Rofecoxib versus naproxen	2.24 (1.24-4.02) 1.55 (0.55-4.36) 2.93 (1.36-6.33)

Unlike the previous meta-analyses by Reicen and Konstam, the Juni meta-analysis analyzed aggregated study-level data, evaluated the effects of variables related to methodologic quality (allocation concealment and use of an external endpoint committee), and assessed the outcome of myocardial infarction (rather than composite cardiovascular endpoints, which could have diluted the effects on myocardial infarction rates). A major point of contention, however, centers on

whether the Juni meta-analysis inappropriately combined results from different control interventions. Although Reicen and others have criticized this method of analysis because different control interventions may be associated with different risks for myocardial infarction,[126] Juni and colleagues' methods appear defensible based on their meta-regression analyses for potential sources of heterogeneity. They found that the only significant source of variation between study results was related to the use of an independent, external endpoint committee, and not to the type of control intervention. For studies with an external endpoint committee, the relative risks for myocardial infarction for rofecoxib compared with placebo, non-naproxen NSAIDs, or naproxen were 2.31, 2.98, and 3.72, respectively, with overlapping confidence intervals (p=0.41 for interaction).[125] The Reicen and Konstam meta-analyses did not assess the effects of this potential source of bias. Other criticisms of Juni have centered on its exclusion of two Alzheimer's trials (discussed below) and on some of its statistical methods (such as adding 0.5 to both arms of a trial when no events occurred in one of the arms). However, Juni and colleagues appeared to follow pre-specified inclusion criteria (trials of patients with musculoskeletal disease), and the statistical methods for dealing with empty cells meet current standards for conducting meta-analysis.[127] A post-hoc re-analysis of the Juni study sponsored by the manufacturer of rofecoxib and criticizing its methods and conclusions is available on-line, but has not been published in the peer-reviewed literature.[128]

A fourth, fair-quality meta-analysis evaluated the cardiovascular risks of selective versus non-selective NSAIDs.[129] However, it only reported results for all COX-2 inhibitors pooled together. It is discussed in the section on cardiovascular risks associated with non-selective NSAIDs.

Rofecoxib versus placebo. The manufacturer-funded meta-analyses by Konstam and Reicin found no significant differences in cardiovascular risk between rofecoxib and placebo.[122, 123] In the Konstam analysis, the relative risk of cardiovascular events (cardiovascular, hemorrhagic, or unknown death; nonfatal yocardial infarction; and nonfatal stroke) was 0.85 (95% CI 0.51 to 1.38).[122] A total of 33 cardiovascular events were reported in the rofecoxib arms. In the Reicin analysis, the incidence of thrombotic cardiovascular AEs was 2.71/100 patient-years in the rofecoxib group and 2.57/100 patient-years in the placebo group (7 events reported in the rofecoxib arms).[123] There were too few events to evaluate the risk of myocardial infarction alone: 3 in the rofecoxib arms in one meta-analysis[123] and 19 fatal and nonfatal myocardial infarctions or resuscitated cardiac arrests in the other.[122] In the Juni meta-analysis, the relative risk for myocardial infarction with rofecoxib relative to placebo was 1.04 (95% CI 0.34 to 3.12) when all trials were pooled, but 2.31 (95% CI 0.49 to 10.82) in trials with an external endpoint committee.[125]

In two subsequent trials of cognitively impaired adults, rates of thrombotic vascular events were similar for rofecoxib 25 mg and placebo.[130, 131] Four thrombotic vascular events (myocardial infarction not reported separately) occurred in 321 patients randomized to rofecoxib (1.2%) compared to 11 of 327 (3.4%) randomized to placebo in one 12-month trial of 692 patients (mean age=75.5 years) with mild to moderate Alzheimer's dementia.[130] In the second trial, 38 of 723 patients with mild cognitive impairment randomized to rofecoxib (5.2%) and 36 of 728 randomized to placebo (4.9%) had a confirmed serious thrombotic vascular event after 115-130 weeks (mean age=74.9 years); the number of confirmed nonfatal myocardial infarctions was 13 versus 10.[131] However, more deaths occurred in the rofecoxib group in this trial (24 or 3.3% versus 15 or 2.1%).

On the other hand, in another long-term (the Adenomatous Polyp Prevention on Vioxx, or APPROVe) trial of a different population—that of patients receiving rofecoxib for prevention of colon polyps—rofecoxib 25 mg/day was associated with an increased risk of cardiac events (myocardial infarction, sudden death from cardiac causes, or unstable angina pectoris) relative to placebo (RR 2.80, 95% CI 1.44 to 5.45).[132] Though the rate of events appeared to diverge only after 18 months in the initially published report,[132] a subsequent analysis that included adverse events originally censored because they occurred more than 14 days after discontinuation of therapy suggests that the curves began to diverge by 4 to 6 months.[133] The risk of cerebrovascular events and peripheral vascular events were not significantly higher on rofecoxib (RR 2.32, 95% CI 0.89 to 6.74 and 0.46, 95% CI 0.08 to 2.03, respectively). Reasons for the discordant findings between the APPROVe and the Alzheimer's trials are unclear but could be related to differential underlying risk in the populations studied, duration of exposure, or differential use of aspirin or other antiplatelet agents.

The most recent and comprehensive meta-analysis included 37 placebo-controlled trials of rofecoxib.[129] It includes data from the trials evaluated in the earlier meta-analyses[122-124] as well as newer information from the long-term polyp prevention and cognitive impairment trials. Much of the data regarding cardiovascular event rates were obtained by requesting unpublished data from trial sponsors. The meta-analysis was rated fair quality because it did not adequately assess the quality of included trials. Rofecoxib was associated with greater risks relative to placebo for the outcomes "any vascular event" (1.5% or 98/6638 versus 1.1% or 72/6415, RR 1.38, 95% CI 1.01 to 1.87) and myocardial infarction (0.8% or 54/6638 versus 0.5% or 30/6415, RR 1.76, 95% CI 1.14 to 2.73), but not for the outcomes stroke or vascular death. This is equivalent to approximately one additional myocardial infarction per 289 patients exposed to rofecoxib for one year instead of placebo. About 85% of the vascular events occurred in patients on a 25 mg dose of rofecoxib. Approximately 40% (21 of 54) of the myocardial infarctions were from the APPROVe trial.[132]

Table 6. CV events in trials of rofecoxib versus placebo: meta-analyses

Study	Outcome	Number of events	Relative risk for (95% CI)
Konstam, 2001[122]	Combined cardiovascular events	33	0.84 (0.51-1.38)
Reicin, 2002[123]	Combined cardiovascular events	7	1.42 (0.24-6.22)
Juni, 2004[125]	Myocardial infarction	Not reported	1.04 (0.34-3.12); all trials 2.31 (0.49 -10.82); only trials with external endpoint committee
Kearney, 2006[129]	Myocardial infarction	54	1.76 (1.14-2.73)

Celecoxib. Five meta-analyses (three funded by the manufacturer of celecoxib[62, 134, 135]) have analyzed the cardiovascular risks associated with celecoxib in primarily unpublished trials.[62, 129, 134-136] The first, a fair-quality study by White and others, included 13 new drug application studies and two large post-marketing trials (CLASS and SUCCESS) of 18,942 patients randomized to celecoxib with osteoarthritis or rheumatoid arthritis.[134] Only two of the 15 trials were longer than 12 weeks in duration. The meta-analysis did not provide enough information about the design of the included studies to judge their quality. A total of 25 cardiovascular events (0.8%) and 6 myocardial infarctions (0.2%) occurred in patients randomized to celecoxib.

There were no differences in risk of cardiovascular events (cardiovascular, hemorrhagic and unknown deaths; nonfatal MI, or nonfatal stroke), fatal myocardial infarction, or nonfatal myocardial infarction between patients randomized to celecoxib versus those randomized to placebo, all NSAIDs, or naproxen (Table 7). There were also no differences in the subgroup of patients who were aspirin non-users. The authors did not perform an analysis of risk associated with different doses of celecoxib.

Table 7. CV events in trials of celecoxib: meta-analysis of 15 trials in patients with arthritis [134]

Comparison	Relative risk for cardiovascular, hemorrhagic and unknown deaths; nonfatal MI; or nonfatal stroke (95% CI)
All patients	
Celecoxib versus placebo	0.85 (0.23 to 3.15)
Celecoxib versus all NSAIDs	1.06 (0.70 to 1.61)
Celecoxib versus naproxen	0.85 (0.29 to 2.46)
Aspirin nonusers	
Celecoxib versus placebo	0.60 (0.11 to 3.29)
Celecoxib versus all NSAIDs	0.86 (0.48 to 1.56)
Celecoxib versus naproxen	0.82 (0.18 to 3.70)

A second, more comprehensive meta-analysis was presented to the FDA's Arthritis Advisory Committee in February 2005.[135] It included 41 trials of celecoxib (N=24,933) for chronic conditions; 33 of the trials were in patients with osteoarthritis or rheumatoid arthritis. Only four of the 41 trials were longer than 12 weeks in duration. The investigators used full follow-up data from the CLASS trials (2,320 patient-years for 3,987 patients). In addition to the composite outcome of any cardiovascular thromboembolic event, the analysis also reported separate analyses for myocardial infarction, stroke, and peripheral vascular events. Over 80% of the cardiovascular events occurred in three large trials: CLASS (N=7,968), SUCCESS (N=13,194), and CAESAR (N=916) (the latter trial remains unpublished). The methods and limitations of this study were similar to the White meta-analysis. There were no significant differences between celecoxib and comparators for myocardial infarction, though event rates were low: only nine myocardial infarctions occurred among 7,462 celecoxib-exposed patients (0.12%) in the placebo-controlled trials. There were also no significant differences for any other cardiovascular thromboembolic event.

Table 8. CV events in trials of celecoxib: meta-analysis of 41 trials[135]

Comparison	Relative risk for myocardial infarction (95% CI)
All patients	
Celecoxib >=200 mg/day versus placebo	1.58 (0.92-2.72)
Celecoxib >=200 mg/day versus non-selective NSAIDs	1.65 (0.38-7.21)
Aspirin nonusers	
Celecoxib >=200 mg/day versus placebo	1.40 (0.61-3.21)
Celecoxib >=200 mg/day versus non-selective NSAIDs	1.64 (0.17-15.33)

Another meta-analysis of manufacturer-held reports of 31 trials by Moore and colleagues found that celecoxib was not associated with a significantly increased risk for myocardial infarction compared with non-selective NSAIDs, any active comparator (including rofecoxib or

paracetamol), any comparator (including placebo), or any non-coxib comparator using a fixed-effect model in patients with rheumatoid or osteoarthritis, though trends towards increased risk were present (Table 9).[62] The overall proportion of patients randomized to celecoxib with myocardial infarction was less than 0.3% (fewer than 60 cases in the largest comparison). There were too few myocardial infarctions in the celecoxib arms of trials comparing celecoxib to placebo (10 events), paracetamol (0 events), or rofecoxib (1 event) to analyze differences in risk. In the two largest trials included in the meta-analysis (CLASS and SUCCESS-I), myocardial infarctions occurred in 0.23% (29 of 12,787) of patients randomized to celecoxib 200 to 800 mg and in 0.18% (15 of 8,375) randomized to a non-selective NSAID (RR 1.7, 95% CI 0.88 to 3.2).

Although this study appears to adhere to high standards for conducting meta-analysis, its results are not verifiable because it analyzed publicly inaccessible data. In addition, myocardial infarctions in the included trials were as reported by investigators, and not subject to adjudication. The duration of exposure to celecoxib in the trials varied, with a mean of about 7 months. The authors of the meta-analysis were unable to perform an analysis on effects of duration of exposure, because the trial reports generally did not provide sufficient information on median duration of use.

Table 9. MI's in trials of celecoxib: meta-analysis of 31 trials in patients with arthritis[62]

Comparison	Relative risk for myocardial infarction
Celecoxib 200 or 400 mg/day versus NSAID	1.9 (0.87 to 4.1)
Celecoxib any dose versus NSAID	1.6 (0.93 to 2.6)
Celecoxib any dose versus any active comparator	1.4 (0.87 to 2.3)
Celecoxib any dose versus any comparator	1.4 (0.88 to 2.2)
Celecoxib any dose versus non-coxib comparator	1.4 (0.88 to 2.2)

A fourth meta-analysis of CV risk associated with celecoxib (not funded by the manufacturer) was less comprehensive because it did not have access to all of the trial data.[136] It limited its analysis to trials that were at least 6 weeks duration and reported cardiovacular events in published articles or publicaly available material on the FDA or manufacturer website, and also differed from the Moore analysis by including trials of patients receiving celecoxib for colon polyp prevention and Alzheimer's disease. It found that the risk of myocardial infarction was increased in 3 trials (APC, ADAPT, PreSAP; none of arthritis patients) comparing celecoxib to placebo (OR 2.26, 95% CI 1.0 to 5.1) and in 5 trials (APC, CLASS, ADAPT, PreSAP, VACT; the latter 2 of arthritis patients) comparing celecoxib to placebo, diclofenac, ibuprofen, or paracetamol (OR 1.88, 95% CI 1.15 to 3.08) (Table 10). No heterogeneity was present. There was no association between celecoxib use and either cerebrovascular events, cardiovascular death, or composite cardiovascular events. Although this study was rated good quality, lack of comprehensiveness is a concern because it excluded 42 celecoxib trials either because they were shorter than 6 weeks or because publicly available information on cardiovascular events was not available. In addition, nearly two-thirds (18 of 29) of the myocardial infarctions in the placebo-controlled trials (the primary analysis) came from the APC (polyp prevention) trial. On the other hand, the meta-analysis also did not include the recently published, large (N=13,274), 12-week SUCCESS-I Study, which reported results consistent with its findings (10 myocardial infarctions or 0.55/100 patient-years in the combined celecoxib arms versus 1 myocardial infarction or 0.11/100 patient-years in the combined non-selective NSAID arms).[63]

Table 10. MI's in trials of celecoxib: meta-analysis of trials of at least 6 weeks duration with published or publicly available data[136]

Comparison	Relative risk for myocardial infarction
Celecoxib any dose versus placebo (3 trials)	2.3 (1.0 to 5.1)
Celecoxib any dose versus placebo, diclofenac, ibuprofen, or paracetamol	1.9 (1.2 to 3.1)

The fifth meta-analysis (also not funded by the manufacturer) analyzed data from 41 published and unpublished trials of celecoxib (8,976 patient-years of exposure).[129] Nine of the trials were longer than 12 weeks in duration. Characteristics of this study, which also evaluated cardiovascular risks associated with other selective and non-selective NSAIDs, are discussed in the rofecoxib section above. Data on celecoxib risk primarily came from patients with osteoarthritis or rheumatoid arthritis (33 trials), but studies of low back or temporamandibular joint pain, ankylosing spondilitis, Alzheimer's disease, and colon polyp prevention were also included. Myocardial infarction rates were higher with celecoxib relative to placebo (0.5% or 44/8976 person-years versus 0.2% or 9/4953, RR 2.13, 95% CI 1.20 to 3.80), and for combined vascular events (0.9% vs. 0.6%, RR 1.51, 95% CI 1.02 to 2.24), but there were no significant differences in risk of stroke alone or vascular death (Table 11). This is equivalent to approximately one additional myocardial infarction for every 325 patients treated with celecoxib instead of placebo for one year. The 99% confidence interval (reported in the article because of multiple subgroup analyses) remained significant for myocardial infarction, but not for combined vascular events. Two large polyp prevention trials accounted for about 60% (27 of 44) of the myocardial infarctions in patients randomized to celecoxib.[109] A trend towards increased risk of vascular events (p=0.03) with higher doses of celecoxib was present, but nearly all of the events at the highest (800 mg daily) dose occurred in the polyp prevention trials. Analyses on the effects of duration and independent event adjudication were not stratified by specific COX-2 inhibitor, nor were estimates of cardiovascular risk with specific COX-2 inhibitors relative to naproxen or non-naproxen NSAIDs (see section on CV risk of non-selective NSAIDs).

Table 11. CV events in trials of celecoxib: meta-analysis of 41 trials of at least 4 weeks duration[129]

Comparison	Outcome	Relative risk (95% CI)
Celecoxib any dose versus placebo	Any vascular event	1.5 (1.0 to 2.2)
Celecoxib any dose versus placebo	Myocardial infarction	2.1 (1.2 to 3.8)
Celecoxib any dose versus placebo	Stroke	1.1 (0.6 to 2.2)
Celecoxib any dose versus placebo	Vascular death	1.3 (0.6 to 2.8)

The estimates of risk for myocardial infarction with celecoxib relative to placebo in the non-manufacturer-funded meta-analyses[129, 136] are higher than in the manufacturer-funded meta-analyses.[134, 135] The major reason for the difference in estimates appears to be the inclusion of two recent, long-term trials of colon polyp prevention (APC and PreSAP) in the former.[108, 110] A large number of myocardial infarctions occurred in these trials (27, compared to a total of nine in the most comprehensive manufacturer-funded meta-analysis[135]), and estimates of risk from both trials were higher than previous pooled estimates without these trials (RR 1.58, 95% CI 0.92 to 2.72).[135] In one meta-analysis,[129, 136] the rate of nonfatal myocardial infarction was 1.3% (18/1356) with celecoxib (200 or 400 mg twice daily) versus 0.4% (3/679) with placebo (RR

2.67, 95% CI 0.5 to 8.41) in the APC trial[108] and 1.0% (9/933) versus 0.5% (3/628) for a relative risk of 1.84 (95% CI 0.54 to 6.28) in PreSAP (400 mg once daily).[110] A subsequent analysis of the APC trial and PreSAP using slightly different data (due to the identification of additional events after study closure) reported a pooled relative risk of 1.9 (95% CI 1.1 to 3.1, no heterogeneity) for the composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or heart failure.[109] Rates of fatal or nonfatal myocardial infarction in were 1.6% (22/1356) versus 0.4% (3/679) in the APC trial and 9/933 (1.0%) vs. 4/628 (0.6%) in PreSAP.

In summary, celecoxib appears associated with an increased risk of myocardial infarctions or thromboembolic cardiovascular events relative to placebo. Much of the evidence for increased cardiovascular risk comes from two large, long-term polyp prevention studies comparing celecoxib 200 or 400 mg twice daily, or 400 mg once daily to placebo. Although trends toward increased myocardial infarction risk with celecoxib relative to placebo as well as relative to other NSAIDs are also present in meta-analyses of primarily short-term trials of arthritis patients, small numbers of events limit the precision of estimates from those trials.

Observational Studies of GI and CV Safety

Overview. Numerous long-term observational studies have evaluated the GI and CV risks associated with selective and non-selective NSAIDs. The studies primarily relied on claims data or other administrative databases or on electronic medical record data collected in practice networks to identify cases, and prescription claims to determine exposure. A strength of these studies is that they evaluated much larger populations than could be enrolled into clinical trials.[137] In addition, they reflect how coxibs and other NSAIDs are actually used in practice better than many clinical trials, which are usually short term, require rigid dosing regimens, limit the use of other drugs, and implement strategies to monitor and enhance compliance. Population- and practice-based studies may also better represent patients who would be excluded from randomized trials because of comorbidities, age, or other factors.

On the other hand, the most important weakness of observational studies is that patients are allocated treatment in a non-randomized matter. This can lead to biased estimates of effects even when appropriate statistical adjustment on a variety of confounding variables is performed.[40] In addition, data sources typically cannot reliably assess over-the-counter aspirin, NSAIDs, or acid-suppressing medication use,[137] and information on prescription fills may not always accurately correspond to the actual degree of exposure to the drugs.

Rofecoxib. Five observational studies reported rates of serious GI events for rofecoxib relative to celecoxib, NSAIDs, and non-use.[138-142](Table 12). In direct comparisons, rofecoxib was associated with a similar risk of upper GI complications compared to meloxicam,[140] but a greater risk of upper GI hemorrhage than celecoxib, non-selective NSAIDs, and diclofenac plus misoprostol.[139, 142] In a nested case-control study, the risk of upper GI bleeding was modestly higher for rofecoxib compared to celecoxib, NSAIDs, or non-use (RR in the range of 1 to 2.)[138] Another case-control study that reported higher relative risks of serious GI events with rofecoxib should be interpreted with caution because exposure information was ascertained using unblinded patient interviewing, which is more susceptible to recall bias than blinded coding of exposures status from prescription or general practice databases.[141]

Analyses of the effects of exposure duration, dosage, and study duration on risk of serious GI events were generally not reported. In fact, COX-2 dosages were only reported in one study

which reported that the proportion of patients on celecoxib receiving >200 mg/day was 19%, and the proportion of patients on rofecoxib on >25 mg/day was 8%.[139]

Table 12. Serious GI events in observational studies

Author, Year Study design Sample size	Mean age (yrs)	Duration (days)	Outcome	Main findings
Hippisley-Cox 2005[138] Case-control Cases: 9407	NR; ≥ 25	Unclear	Complicated GI event	↑ *risk relative to non-use:* No for celecoxib (RR 1.25; 95% CI 0.91, 1.72) Yes for rofecoxib (RR 1.79; 95% CI 1.42, 2.26); overall selective (RR 1.72; 95% CI 1.29, 2.29) and non-selective NSAIDs (1.67; 95% CI 1.43, 1.94); ibuprofen (RR 1.58; 95% CI 1.37, 1.83); diclofenac (RR 2.07; 95% CI 1.82, 2.35); naproxen (RR 1.97; 95% CI 1.48, 2.61)
Mamdani 2002[139] Cohort n=143,969	75.7	141	Upper GI hemorrhage	↑ *risk relative to celecoxib:* Yes for rofecoxib (RR 1.9; 95% CI 1.2, 2.8), non-selective NSAIDs (RR 1.9; 95% CI 1.0, 3.5) and diclofenac+ misoprostol (RR 3.2; 95% CI 1.6, 6.5)
Layton 2003[140] Cohort n=34,355	60.4-62.5	270	Upper GI complications (perforations/bleeding)	Similar risk for rofecoxib and meloxicam (RR 0.91; 95% CI 0.59, 1.42)
Laporte 2004[141] Case-control Cases=2,813	NR; ≥ 18	NR	Upper GI bleeding	↑ *risk vs. non-use* for rofecoxib (RR 7.2; 95% CI 2.3, 23.0), diclofenac (RR 3.7; 95% CI 2.6, 5.4), ibuprofen (RR 3.1; 95% CI 2.0, 4.9), indomethacin (RR 10.0; 95 % CI 4.4, 22.6), ketoprofen (RR 10.0; 95% CI 3.9, 25.8), ketorolac(RR 24.7; 95% CI 8.0, 77.0), meloxicam (RR 5.7; 95% CI 2.2, 15.0), naproxen (RR 10.0; 95 % CI 5.7, 17.6), nimesulide (RR 3.2; 95% CI 1.9, 5.6), piroxicam (RR 15.5; 95% CI 10.0, 24.2)
Kasliwal 2006[142] Cohort n=32,726	62.5	Median Rofecoxib=111 Celecoxib=90 p<0.0001	Upper GI complications (perforations/bleeding)	Rofecoxib versus celecoxib aRR (95% CI): 1.60 (0.95, 2.70)

Fourteen observational studies evaluated the risk of cardiovascular events associated with rofecoxib (Table 13).[142-155] Interpretation of the studies is complicated by the use of different study designs, adjustment for different confounders, and evaluation of different populations and outcomes. Six of these studies appeared to rely exclusively on administrative and pharmaceutical databases to determine outcomes, exposures, and comorbidities.[143, 147, 149-152] The other studies supplemented administrative or claims data with chart review;[145, 153] clinical or practice-based databases,[146, 148, 155] or telephone interviews.[144] An interim analysis of one study relied on a combination of a medication surveillance database, physician questionnaires, hospital admission data, spontaneous reports, and national morbidity and mortality databases.[154]

Several studies indicate that using claims data is quite accurate (positive predictive value >90%) for identifying myocardial infarction.[156, 157] A weakness of relying exclusively on administrative databases, however, is that they frequently have incomplete information about potentially important confounders such as income level, obesity, smoking status, and level of

education.[157] All three of the observational studies that collected information about body mass index, for example, supplemented administrative databases with other sources.[144-146] Unmeasured confounders could result in less accurate estimates of cardiovascular risk, though one analysis suggests that the effects would be only modest.[158] On the other hand, studies can also 'overcontrol' if they attempt to adjust for cardiovascular risk factors identified after the initiation of treatment, when the risk factors are actually intermediate effects of the drugs themselves that predispose to subsequent cardiovascular events.[159]

Rofecoxib was associated with an increased risk of CV events relative to non-selective NSAIDs in three of five studies[40, 144, 152, 153] and an increased risk relative to celecoxib in three of five studies.[142, 144, 145, 154, 160] In studies that compared rofecoxib, celecoxib, or NSAID use to non-use, none of the drugs were consistently associated with increased risk of CV events.[143, 146, 147, 149, 151, 155] CV event risk estimates from two observational studies of rofecoxib relative to naproxen (Solomon 2004[145]: OR 1.17, 95% CI 0.90, 1.52; Kimmel 2005[144]: OR 3.30, 95% CI 1.37, 8.40) were lower than the estimated relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen in VIGOR.[103] It is likely that the inconsistencies in effect magnitudes were due in large part to population differences and study methodology. For example, risk estimates from the Solomon 2004 study[145] may only be generalizable to a population that is of a more advanced age than that of VIGOR (81.6 vs. 58 years) and of a possibly lower income level, as it focused on low-income Medicare beneficiaries. Participants in the Kimmel 2005 study,[144] on the other hand, were similar in mean age to those in VIGOR (53.1 vs. 58 years), but different methods of data ascertainment may have affected risk estimates. This study, which found the highest risk of MI associated with rofecoxib compared with celecoxib (OR 2.72), differed from the others in that it collected information about exposures and covariates using structured telephone interviews rather than by using administrative or large practice databases.[144] The use of structured telephone interviews could have enhanced the ability of the investigators to measure relevant confounders and drug exposures. On the other hand, participation bias (only 50% of those approached participated) and recall bias could have skewed the results, though it is not clear that such biases should favor either rofecoxib or celecoxib.

Results of studies that found similar risk of CV events with rofecoxib and meloxicam[152] or celecoxib[142, 154] may also be less reliable. These studies adjusted for far fewer demographic and prognostic factors than other studies that adjusted for multiple demographic factors and comorbidities.

Another factor that varied between studies was how exposure status was defined. In one of the studies that reported no association between rofecoxib use and cardiovascular thrombotic events, use of selective COX-2 inhibitors was defined as prescriptions within 6 months of the index date.[150] By contrast, other studies defined current use as occurring on or near the index date, which strengthens confidence in inferences about the link between rofecoxib and the observed MIs.

Table 13. Cardiovascular events in observational studies

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Levesque 2005[143] Cohort n=59724	NR; ≥ 66	22.50%	844.8	***Acute MI, fatal or nonfatal*** ↑ *risk relative to NSAID non-use:* Yes for rofecoxib, regardless of dose (Overall RR 1.24; 95% CI 1.05, 1.46) No for celecoxib (Overall RR 0.99; 95% CI 0.85, 1.16), naproxen (RR 1.17; 95% CI 0.75, 1.84) or meloxicam (95% CI 1.06; 95% CI 0.49, 2.30)
Kimmel 2005[144] Case-control Cases: 1718	NR; aged 40 to 75	33.60%	NR	***Nonfatal MI*** ↑ risk for rofecoxib when directly compared with celecoxib (OR 2.72; 95% CI 1.24 to 5.95) or naproxen (OR 3.39; 95% CI 1.37, 8.40) ↑ risk for rofecoxib* relative to ibuprofen or diclofenac (OR 2.04; 95% CI 1.16, 3.60) or naproxen (OR 3.30; 95% CI 1.37, 8.40) Risk for celecoxib* similar to ibuprofen or diclofenac (OR 0.77; 95% CI 0.4, 1.48) or naproxen (OR 0.81; 95% CI 0.37, 1.77) *Regardless of aspirin use
Solomon 2004[145] Case-control Cases=10,895	NR; > 80	NR	1-30 days 31-90 days > 90 days	***Acute MI*** ↑ risk for rofecoxib relative to celecoxib (OR 1.24; 95% CI 1.05, 1.46) Risk for rofecoxib similar to naproxen (aOR 1.17; 95% CI 0.9, 1.52) or ibuprofen (aOR 1.21; 95% CI 0.92, 1.58) or other NSAIDs (aOR 1.17; 95% CI 0.99, 1.38) Risk for celecoxib similar to naproxen (aOR 0.95; 95% CI 0.74, 1.21) or ibuprofen (aOR 0.98; 95% CI 0.76, 1.26) or other NSAIDs (aOR 0.95, 95% CI 0.82, 1.10)
Hippisley-Cox 2005[146] Case-control Cases: 9218	NR; aged 25-100	NR	NR	***First ever MI*** ↑ risk relative to nonuse: Yes for rofecoxib (aOR 1.32; 95% CI 1.09, 1.61), other selective NSAIDs (aOR 1.27; 95% CI 1.00, 1.61), ibuprofen (aOR 1.24; 95% CI 1.11, 1.39), diclofenac (aOR 1.55; 95% CI 1.39, 1.72), naproxen (aOR 1.27; 95% CI 1.01, 1.60) and other non-selective NSAIDs (aOR 1.21; 95% CI 1.02, 1.44) No for celecoxib (aOR 1.21; 95% CI 0.96, 1.54)
Mamdani 2003[147] Cohort n=166,964	NR; ≥ 66	14.70%	165.6	***Incidence of hospitalization for acute MI: risk relative to non-use*** Similar risk for rofecoxib (aRR 1.0; 95% CI 0.8, 1.4), celecoxib (aRR 0.9; 95% CI 0.7, 1.4), naproxen (aRR 1.0; 95% CI 0.6, 1.7), or non-naproxen non-selective NSAIDs (aRR 1.2; 95% CI 0.9, 1.4)
Graham 2005[160] Case-control Cases=8,143	NR: 18-84	Telephone interview subgroup (n=817): 23%	Mean=113 days before event	***Acute MI requiring admission or sudden cardiac death: risk relative to celecoxib*** ↑ risk for rofecoxib for all dosages (aOR 1.59; 95% CI 1.10, 2.32) or for dosages > 25 mg (aOR 3.58; 95% CI 1.27, 10.11), but dosages ≤ 25 mg had risk similar to celecoxib (aOR 1.47; 95% CI 0.99, 2.17) ↑ risk for ibuprofen (aOR 1.26; 95% CI 1.00, 1.60), naproxen (aOR 1.36; 95% CI 1.06, 1.75), or other NSAIDs (aOR 1.35; 95% CI 1.06, 1.72)

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Johnsen 2005[149] Case-control Cases=10,280	69.6	6.9% high dose	NR	***Acute MI**: risk relative to nonusers* ↑ *risk* current (aRR 1.80; 95% CI 1.47, 2.21)and new users (aRR 2.52; 95% CI 1.45, 3.13) of rofecoxib ↑ risk for new users of celecoxib (aRR 2.13; 95% CI 1.45, 3.13) and similar risk for current and non-users of celecoxib (aRR 1.25; 95% CI 0.97, 1.62) Similar risk for new (aRR 1.65; 95% CI 0.57, 4.83) or current users of naproxen (aRR 1.50; 95% CI 0.99, 2.29) relative to nonuse ↑ risk for new (aRR 2.65; 95% CI 2.00, 3.50) or current users of other nonaspirin NSAIDs (aRR 1.68; 95% CI 1.52, 1.85) naproxen (aRR 2.13; 95% CI 1.45, 3.13) and similar risk for current and non-users of celecoxib (aRR 1.25; 95% CI 0.97, 1.62)
Shaya 2005[150] Cohort n=6,250 50% black	NR; 70% were aged 50 years or younger	NR	≥ 60 prior to event	***Cardiovascular thrombotic events: relative to non-naproxen NSAIDs*** Similar for rofecoxib (aOR 0.99; 95% CI 0.76, 1.30) or celecoxib (aOR 1.19; 95% CI 0.93, 1.51)
Ray 2002[161] Cohort n=378,776	61.5	NR	NR	***Serious CHD (hospital admission for AMI or death from CHD)**: relative to non-use* *Similar risks for rofecoxib at dosages ≤ 25 mg (aIRR 1.03; 95% CI 0.78, 1.35) or > 25 mg (aIRR 1.70; 95% CI 0.98, 2.95), celecoxib (aIRR 0.96; 95% CI 0.76, 1.21), ibuprofen (aIRR 0.91; 95% CI 0.78, 1.06), or naproxen (aIRR 0.93; 95% CI 0.82, 1.06 relative to nonuse*
Layton 2003[152] Cohort n=34,355	NR	NR	270	***Thromboembolic events: Rofecoxib vs meloxicam*** (A) cardiovascular: similar risk (RR 1.38; 95% CI 0.71, 2.67) ;(B) cerebrovascular: increased risk with rofecoxib (RR 1.68; 95% CI 1.15, 2.46) (C) peripheral venous thrombotic: lower risk for rofecoxib (RR 0.29; 95% CI 0.11, 0.78)
Velentgas 2005[153] Cohort n=424,584	NR (40-64 years)	NR	5.1 months	***Combined endpoint of acute coronary syndrome and myocardial infarction: risk relative to ibuprofen or diclofenac (adjusted rate ratios)*** Increased risk for current use of rofecoxib (1.35; 95% CI 1.09, 1.68) and but not for recent use (1.15; 95% CI 0.88, 1.50) No increased risk for current (1.03; 95% CI 0.83, 1.27) or recent use of celecoxib (0.91; 95% CI 0.70, 1.17) No increased risk for current (1.14 95% CI 0.93, 1.39) or recent use of naproxen (0.86; 95% CI 0.70, 1.04)
Harrison-Woolrych 2005[154] Cohort *Interim* analysis of 11,149 of 58,849 who completed follow-up by 11/30/04	NR	NR	NR	***Thrombotic cardiovascular events*** Celecoxib and rofecoxib were associated with similar risks (aHR 0.94; 95% CI 0.51, 1.70)

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Andersohn 2006[155] Case-control Cases=3,643	68.7	NR	Mean=542 days	***aRR (95% CI) for diagnosis of AMI, death from AMI, or sudden death from coronary heart disease (CHD) relative to nonuse:*** Increased risk for celecoxib 1.56 (1.23, 1.98), rofecoxib 1.33 (1.06, 1.67), etoricoxib 2.02 (1.08, 3.80) and diclofenac 1.36 (1.17, 1.58) No increased risk for valdecoxib 4.26 (0.60, 30.27), ibuprofen 1.00 (0.83, 1.21) or naproxen 1.16 (0.86, 1.58)
Kasliwal 2006[142] Cohort n=32,726	62.5	Rofecoxib=35.3% Celecoxib=21.9% P<0.0001	Median Rofecoxib=111 Celecoxib=90 p<0.0001	aRR (95% CI) for rofecoxib versus celecoxib (adjusted for age, age2, sex, and concomitant use of the combination of aspirin and/or antiplatelet/anticoagulant agents (a) Cardiovascular TE: 1.04 (0.50, 2.17) (b) Cerebrovascular TE: 1.43 (0.86, 2.38) (c) Peripheral venous (DVT/PE): 0.36 (0.01, 1.34)

aOR=adjusted odds ratio; aRR=adjusted relative risk; aIRR=adjusted incidence rate ratios; aHR=adjusted hazard ratio; CI=confidence interval

Celecoxib. As summarized above, celecoxib was consistently associated with lower risks of serious GI[139] and CV events[144, 145, 160] than rofecoxib in several observational studies. Observational studies also demonstrated that, compared with non-selective NSAIDs, celecoxib was consistently GI protective[139, 162] or neutral[138] and was never associated with higher risks of CV events.[144, 145, 150, 160]

Specifically, with regard to GI safety, celecoxib was associated with significantly lower risks of GI hemorrhage when directly compared to non-selective NSAIDs (relative risk 0.23, 95% CI 0.12, 0.43)[139] and of perforation or bleeding compared to meloxicam (RR 0.56; 95% CI 0.32, 0.96).[162] Risk of complicated GI events was significantly lower for NSAID nonuse relative to numerous NSAIDs (i.e., selective NSAIDs, ibuprofen, diclofenac, naproxen, non-selective) but was similar relative to celecoxib.[138]

With regard to CV safety, celecoxib was associated with similar risks (estimate range 0.77 to 1.19) of serious CV events compared to ibuprofen, diclofenac, naproxen, and "other NSAIDs"[144, 145, 150] and, in one study, was associated with significantly lower risks of acute MI requiring admission or sudden cardiac death than ibuprofen, naproxen, or other NSAIDs.[160]

Relative to non-use, some observational studies have shown an increased risk of MI associated with celecoxib[149, 155], whereas others have not.[143, 146, 147] In the two studies that found an association, the increased MI risk was either time-dependent[149] or dose-dependent.[155]

Additional analysis of observational studies. An important limitation of the observational studies is that they did not simultaneously assess the risk for serious cardiac and GI events. We re-analyzed data from three studies that reported rates of acute myocardial infarction,[147] hospital admissions for congestive heart failure,[163] and upper gastrointestinal bleeding[139] in a large cohort of elderly patients in Ontario, Canada, to estimate the net effects of selective and non-selective NSAIDs on serious cardiovascular and GI events in this population. Although the three studies evaluated the cohort at slightly different points in time, study methods and populations characteristics appeared essentially identical.

We calculated the effects of selective and non-selective NSAIDs on numbers of acute myocardial infarction, upper GI bleed, and hospitalization for heart failure using baseline rates of events in patients not exposed to NSAIDs and estimates of risk as reported in the studies (Table 14). We then estimated the net effects on all three serious adverse events using Monte Carlo simulation (see Methods section for additional details).

Table 14. Baseline rates of MI, upper GI bleed, and congestive heart failure (CHF) and risk associated with selective and non-selective NSAIDs in an Ontario cohort of elderly persons

Adverse event	Study, year	Baseline rates (per 1000 person-years)	Risk with celecoxib	Risk with rofecoxib	Risk with non-selective NSAIDs	Risk with naproxen
Myocardial infarction	Mamdani, 2003[147]	8.2	0.9 (0.7 to 1.2)	1.0 (0.8 to 1.4)	1.5 (1.2 to 1.8)	1.0 (0.6 to 1.7)
Upper GI bleed	Mamdani, 2002[139]	2.2	1.0 (0.7 to 1.6)	1.9 (1.3 to 2.8)	4.0 (2.3 to 6.9)	4.0 (2.3 to 6.9)
Heart failure admission	Mamdani, 2004[163]	9.1	1.0 (0.8 to 1.3)	1.8 (1.5 to 2.2)	1.4 (1.0 to 1.9)	1.4 (1.0 to 1.9)

Our results (see Table 15) suggest that in this population, under real-world conditions, use of celecoxib was neutral with regard to these adverse events when compared with non-use. On the other hand, use of rofecoxib, non-selective NSAIDs, and naproxen were all associated with more serious adverse events than they prevented (Table 15). Rofecoxib and naproxen essentially appeared equivalent when considering all three adverse events together, though rofecoxib was associated with more heart failure admissions and fewer GI bleeds. Our estimates are consistent with analyses of serious adverse events in VIGOR (discussed earlier), which found that rates were essentially equivalent for rofecoxib and non-selective NSAIDs.[113, 114] However, the result are discordant from analyses of serious adverse events in CLASS, which found that celecoxib offered no advantage over non-selective NSAIDs.[94, 113] Differences in populations (the Ontario cohort only enrolled patients over 65 years old who filled multiple prescriptions), indications for starting celecoxib, dosing of celecoxib, or co-medication use might account for this discrepancy. In addition, because these studies only included patients who filled multiple prescriptions for NSAIDs, the analyses could underestimate early adverse events.

Table 15. Effects of selective or non-selective NSAIDs on number of serious adverse events

	Estimated effect on MI's (number per 1000 person-years)	Estimated effect on GI bleed (number per 1000 person-years)	Estimated effect on heart failure admissions (number per 1000 person-years)	Net effect on number of MI's, GI bleeds, and heart failure admissions (number per 1000 person-years)
Celecoxib	-0.82 (-2.46 to 1.64)	0 (-0.66 to 1.32)	0 (-1.82 to 2.73)	-0.70 (-3.58 to 2.71)
Rofecoxib	0 (-1.64 to 3.28)	+1.98 (0.66 to 3.96)	+7.28 (4.55 to 10.92)	+9.42 (5.47 to 13.99)
Non-selective NSAIDs	+4.1 (1.64 to 6.56)	+6.6 (2.86 to 12.98)	+3.64 (0 to 8.19)	+14.68 (8.59 to 22.72)
Naproxen	0 (-3.28 to 5.74)	+6.6 (2.86 to 12.98)	+3.64 (0 to 8.19)	+10.77 (3.92 to 19.89)

GI and CV Safety of Valdecoxib

The risk of clinically significant upper GI events (bleeding, perforation, and gastric outlet obstruction) with valdecoxib was evaluated in a fair-quality, manufacturer-funded meta-analysis of eight randomized controlled trials of 12 to 26 weeks duration.[117] This study prospectively defined ulcer complications and used independent adjudication to determine adverse events. However, it is not described how assiduously the trials adhered to the adjudication process. Four of the trials were not published, and there was insufficient information about study design to determine the quality of the trials. The meta-analysis found valdecoxib associated with a significantly lower rate of significant upper GI events compared with non-selective NSAIDs (0.68% vs. 1.96%, all patients; 0.29% vs. 2.08%, non-aspirin users; $p<0.05$). Another meta-analysis of five trials by the same authors found valdecoxib associated with a lower risk of 'moderate-to-severe' upper GI symptoms compared with non-specific NSAIDs (HR 0.59, 95% CI 0.47 to 0.74) and similar risk relative to placebo.[164] Adverse events were self-reported by patients in these trials, and the quality of the trials was not assessed by the meta-analysts. Two of the included trials were published only in abstract form.

We found no published trials evaluating the risk of cardiovascular events associated with valdecoxib in patients with arthritis. Valdecoxib was not associated with an increased risk of cardiovascular events relative to placebo or other NSAIDs in any of three fair-quality meta-analyses of primarily unpublished data. The ability to detect increased cardiovascular risk in all of these meta-anslyses is limited by small numbers of events. A meta-analysis funded by Pfizer and presented to the FDA in February 2005 analyzed primarily unpublished data from 19 trials of patients with chronic pain (methods described above in the section on celecoxib).[135] Thirteen studies were of patients with osteoarthritis or rheumatoid arthritis. Three were longer than 12 weeks in duration. There was no association between valdecoxib use and either cardiovascular thromboembolic events or myocardial infarction (Table 16). However, only 5 of 4,438 patients (0.2%) randomized to valdecoxib in the placebo-controlled trials and 6 of 4,591 (0.1%) in the active-controlled trials had a cardiovascular event. An earlier meta-analysis of 10 trials (also funded by Pfizer, and using similar methods) also found no difference in risk for myocardial infarction between valdecoxib and either placebo or other NSAIDs.[134]

Table 16. Myocardial infarction in trials of valdecoxib for chronic pain: meta-analysis of 19 trials[135]

Comparison	Relative risk for myocardial infarction
Valdecoxib >=10 mg/day versus placebo	1.80 (0.47-6.97)
Valdecoxib >=10 mg/day versus non-selective NSAID	0.32 (0.12-0.87)

The most recent meta-analysis (not funded by the manufacturer) included 14 placebo-controlled trials (Table 17).[129] There were no significant differences between valdecoxib and placebo for the outcomes any vascular event (RR 1.47, 95% CI 0.44 to 4.95), myocardial infarction (RR 1.65, 95% CI 0.28 to 9.87), stroke (RR 0.85, 95% CI 0.07 to 10.6) or vascular death (RR 2.72, 95% CI 0.49 to 15.2). A total of 14 vascular events (1.9%) and 8 myocardial infarctions (1.1%) occurred among the 748 patients in the valdecoxib arms.

Table 17. Cardiovascular events in trials of valdecoxib versus placebo: meta-analysis of 14 trials[129]

Comparison	Outcome	Relative risk
Valdecoxib versus placebo	Any vascular event	1.47 (0.44-4.95)
Valdecoxib versus placebo	Myocardial infarction	1.65 (0.28-9.87)
Valdecoxib versus placebo	Stroke	0.85 (0.07-10.6)
Valdecoxib versus placebo	Vascular death	2.72 (0.49-15.2)

None of the meta-analyses included two short-term (<2 month) trials in the high-risk setting of post-coronary artery bypass surgery.[165,166] In these trials, parecoxib (an intravenous coxib rapidly converted to valdecoxib) followed by valdecoxib (40 mg bid[165] or 20 mg bid[166]) was associated with a two- to three-fold higher short-term risk of cardiovascular events compared with placebo (pooled relative risk 3.08, 95% CI 1.20 to 7.87).[167]

FDA information. A warning was added to the valdecoxib product label in November, 2002. It was prompted by reports of cases of serious anaphylactic reactions and serious dermatologic adverse events in postmarketing surveillance.[168] A study of two large European data sources and the US FDA spontaneous adverse events reporting system prior to the introduction of COX-2 inhibitors found other NSAIDs—in particular piroxicam and tenoxicam—also associated with Stevens-Johnson syndrome and toxic epidermal necrolysis.[169] However, the rates of these events were extremely low, on the order of one per 100,000 or less during an initial 8-week course of therapy.

GI and CV Safety of Etoricoxib

A fair quality meta-analysis of ten RCTs, which included long-term (>1 year) data from 7 trials of OA, RA, or ankylosing spondylitis patients, found etoricoxib at doses ranging from 5 to 120 mg/day (mean dose 87 mg/day) associated with a lower risk of confirmed PUBs (upper GI perforations, symptomatic gastroduodenal ulcers, and upper GI bleeding) compared to diclofenac 150 mg/day, naproxen 1000 mg/day or ibuprofen 2400 mg/day (1.24% vs. 2.48%, RR 0.48, 95% CI 0.32, 0.73).[170] This meta-analysis was rated fair quality because it did not provide adequate detail of the included trials and did not evaluate the effects of dose, duration, or other potential sources of heterogeneity. In addition, it included results of noncomparative extension phases in its analyses, resulting in unequal durations of follow-up for the etoricoxib group (median 12.4 months) compared to the non-selective NSAID groups (median 6.3 months). There were too few events in patients on concomitant aspirin (8 overall) to evaluate its effects on GI safety. An earlier meta-analysis that used similar methods to analyze rates of perforations, symptomatic ulcers, and bleeds reported similar results.[171]

There is only limited evidence regarding the CV risk associated with long-term use of etoricoxib. One 52-week trial reported that no patients randomized to naproxen and five (2%) randomized to etoricoxib (four receiving 90 mg/day; one 120 mg/day) experienced a serious cardiovascular adverse event.[172]

Three meta-analyses have evaluated cardiovascular risks associated with etoricoxib. The largest and most recent meta-analysis (by Kearney and colleagues) included 17 placebo-controlled trials of patients (1,167 person-years of exposure) mainly with osteoarthritis or rheumatoid arthritis.[129] Most of the trials had short (less than 12 weeks) placebo-controlled periods. There was no difference between etoricoxib and placebo for risk of any vascular event (RR 1.78, 95% CI 0.43 to 7.40), myocardial infarction (RR 4.48, 95% CI 0.20 to 99.4), stroke

(RR 1.17, 95% CI 0.21 to 6.51), or vascular death (RR 4.48, 95% CI 0.36 to 56.3). The number of cardiovascular events was very low, with only two myocardial infarctions over 753 person-years of exposure to etoricoxib (0.3%). A less-comprehensive systematic review of five short-term trials (all included in the Kearney meta-analysis) also found no significant increased risk of thromboembolic event (pulmonary embolism, deep vein thrombosis, myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack) with etoricoxib (dose range 30 to 90 mg) versus placebo (OR 1.49, 95% CI 0.42-5.31).[173] A third meta-analysis (available only as an abstract) of 12 trials of unspecified durations found that the cardiovascular safety of etoricoxib compared favorably to placebo and non-selective NSAIDs (RR 1.11, 95% CI 0.32, 3.81 and RR 0.83, 95% CI 0.26, 2.64, respectively) though there was a trend towards increased risk compared to naproxen (RR 1.70, 95% CI 0.91,3.18).[174]

GI and CV Safety of Lumiracoxib

One large (N=18,325), long-term (52 weeks) study of osteoarthritis patients (The Therapeutic Arthritis Research and Gastrointestinal Event Trial, or TARGET) compared the safety of a supratherapeutic dose of lumiracoxib (400 mg/day) to naproxen (1000 mg/day) or ibuprofen (2400 mg/day) over 52 weeks.[175-177] In patients not taking aspirin, lumiracoxib was associated with a lower risk of bleeding, perforation, or obstruction compared to naproxen or ibuprofen (HR 0.21, 95% CI 0.12, 0.37, 1-year incidence of ulcer complications 0.25% vs. 1.09%).[175] There was no difference in ulcer complication risk among aspirin users (HR 0.79, 95% CI 0.40, 1.55). The rate of myocardial infarction was low, ranging from 0.16% to 0.38%, and there were no statistically significant differences between interventions (HR 1.77 for lumiracoxib versus naproxen, 95% CI 0.82, 3.84 and HR 0.66 for lumiracoxib versus ibuprofen, 95% CI 0.21, 2.09).[177]

A recent fair-quality meta-analysis of 12 primarily short-term trials found no significant increase in risk of vascular events (RR 1.13, 95% CI 0.43 to 2.93), myocardial infarction (RR 1.07, 95% CI 0.20 to 5.63), stroke (RR 0.63, 95% CI 0.13 to 3.11), or vascular death (RR 2.55, 95% CI 0.54 to 12.0) with lumiracoxib relative to placebo.[129] The number of events, however, was low, with only five myocardial infarctions among 1375 patients in the lumiracoxib arms (0.4%).

GI and CV Safety: Comparison of NSAIDs

Partially selective NSAIDs. Evidence that meloxicam, nabumetone, and etodolac prevent ulcer complications is weaker than that for coxibs. Meloxicam is the most widely studied of the three drugs and was generally associated with no advantage in GI protection relative to other partially-selective and non-selective NSAIDs or non-use.[143, 178-185] Evidence for nabumetone and etodolac is sparse and insufficient to make reliable judgments about comparative GI and CV safety.

Meloxicam. Risks of serious ulcer complications (perforation, bleeding, or obstruction) and/or MI were reported in one clinical trial of meloxicam[179] and three observational studies.[143, 180, 182] In the single, poor-quality (non-randomized and non-blinded) trial, meloxicam was not associated with significant differences in rates of GI hemorrhage at 6 months relative to other NSAIDs (RR 0.32; 95% CI 0.06, 1.63) in 4,526 rheumatoid arthritis patients seen by family or internal medicine physicians in Germany between August 1996 and July 1997.[179] However,

differences in baseline disease severity could have favored the control group, and it is unclear whether the analyses adjusted for such baseline differences. Estimates of GI and CV risk have also been reported in two recent (2004) cohort studies that followed participants for 14 months[180] and 2.4 years.[143] GI complication-related hospitalizations were similar for meloxicam (0), nabumetone (1, 4.5%), salsalate (1, 5.9%), naproxen (5, 7.9%), and ibuprofen (0) among a cohort of long-term care residents in Indiana (mean age=81.2 years).[180] In a cohort of 59,724 elderly individuals in Quebec, meloxicam (adjusted rate ratio 1.06; 95% CI 0.49, 2.30) and naproxen (1.17; 95% CI 0.75, 1.84) were associated with similar increases in risk of MI relative to non-use.[143] Meloxicam (RR 1.5; 95% CI 0.1, 17.1), naproxen (RR 1.0; 95% CI 0.3, 3.3), and piroxicam (RR 0.7; 95% CI 0.2, 2.3) were also associated with similar nonsignificant risks of MI relative to diclofenac in a nested case-control study using data from the UK GPRD.[182]

Estimates of GI risk as measured by a composite score that included GI tolerability, PUBs, hospitalization or GI-related death outcomes were reported in a good-quality meta-analysis.[183] Compared to non-use, the composite GI risk for meloxicam (RR 1.24; 95% CI 0.98, 1.56) was comparable with that of non-selective NSAIDs. Relative risks of GI hospitalizations or GI-related deaths alone were not reported. Composite GI outcome data from cohort studies were also analyzed in this study and suggested higher risk estimates (combined NSAID RR 2.2, 95% CI 1.7, 2.9) than the trials, but the results were not stratified by individual NSAIDs.

Three meta-analyses focussing only on short-term trials reported PUBs (perforation, symptomatic ulcer, or bleeding) associated with meloxicam. The first meta-analysis included 10 trials (seven double-blinded).[181] Most of the patients were followed for only 4 weeks, and the dose of meloxicam was 7.5 mg in 4 trials and 15 mg in 6 trials. The meta-analysis did not report absolute event rates, but found that the risk of PUBs was reduced in the meloxicam patients (OR 0.52, 95% CI 0.28-0.96) relative to non-selective NSAIDs. A twelve-week double-blind trial of meloxicam 7.5, 15 or 22.5 mg and diclofenac 75 mg bid in RA patients (n=894) published after this meta-analysis found similar PUB rates (1.1%, 0.5%, 0.6%, and 0%, respectively) in all arms.[178] In a more recent meta-analysis funded by the manufacturer of meloxicam and using manufacturer-held documents from 28 trials, there was a dose-response relationship between meloxicam and PUBs as ascertained by a blinded, external adjudication committee.[186] Meloxicam at 7.5 mg was associated with lower PUB rates during the first 60 days compared to diclofenac, piroxicam, or naproxen, but the 15 mg dose was only associated with lower PUB rates than piroxicam. In a third meta-analysis (not yet published) of three short-term (4- to 6-week) trials, there was no difference in the risk of complicated ulcers (perforations, obstructions and bleeds) associated with meloxicam relative to the non-selective NSAIDs piroxicam (two trials[47, 52]) and diclofenac(one trial[49]), with a relative risk of 0.50 (95% CI 0.23, 1.12).[115]

Nabumetone. For nabumetone, a fair-quality meta-analysis of six short-term (3 to 6 months) studies (five published and one abstract) found one PUB event among 4,098 patients taking nabumetone versus 17 events among 1,874 non-selective NSAID patients; this result was highly statistically significant.[187] The absolute PUB rates were about 2 versus 6 per 1,000 patient-years. For comparison, in a similar meta-analysis of rofecoxib studies, the PUB rates per 1,000 patients per year were 13 for rofecoxib and 26 for NSAIDs;[118] it is not clear why the rates of PUBs were so much lower in the nabumetone trials. There was also a significant reduction in treatment-related hospitalizations in the nabumetone group (6.4 per 1,000 patients per year vs. 20.3 per 1,000 patients per year). The results of this meta-analysis are not directly comparable to other trials and meta-analyses that reported complicated ulcers as a separate outcome because

symptomatic ulcers were also included. In addition, the methods used to ascertain the endpoints in the trials were not described in enough detail to determine whether they were accurate and applied consistently. Finally, the similarity of the subjects in the efficacy trials to a broader group of NSAID users could not be determined.

Etodolac. We found no trials reporting rates of serious GI complications in patients taking etodolac. In two observational studies, etodolac was not associated with a lower rate of PUBs compared to non-use[184] or naproxen.[188] In another observational study using data from the UK General Practice Database, the adjusted relative risks of PUB compared with non-use ranged from 2.2 (95% CI 0.4, 11.3) for etodolac to 6.2 (95% CI 3.7, 10.1) for piroxicam and overlapped across all NSAIDs studied.[189] When compared to naproxen using historical data from Dallas Veterans Affairs Medical Center records, etodolac had a GI protective effect for all users (RR 0.24, 95% CI 0.09, 0.63) and for NSAID-naïve users (RR 0.18, 95% CI 0.05, 0.61) only when low-dose aspirin was not taken concomitantly.[188]

Non-selective NSAIDs - GI safety. Randomized controlled trials[115] and observational studies[11, 190, 191] consistently report that non-selective, non-aspirin NSAIDs are associated with increased risks of serious GI events relative to non-use. There is no clear, consistent evidence that any one non-selective, non-aspirin NSAID is any less risky than another.

Preliminary results (not yet published) from a meta-analysis of randomized controlled trials found that selective COX-2 inhibitors as a class (defined by the investigators as celecoxib, rofecoxib, valdecoxib, lumiracoxib, and meloxicam) were associated with lower risks of complicated ulcers (perforation, obstruction, or bleed) when compared with naproxen (0.34; 95% CI 0.24, 0.48), ibuprofen (0.46; 95% CI 0.30, 0.70), and diclofenac (0.31; 95% CI 0.06, 1.61).[115] There were no clear differences among the three non-selective NSAIDs. The validity of these findings, however, cannot be assessed until the full report is published. However, they are consistent with results from a previous meta-analysis in which increased risks of GI complications (major plus minor) were similar for different NSAIDs relative to non-use: indomethacin (RR 2.25; 95% CI 1.01, 5.07), naproxen (RR 1.83; 95% CI 1.25, 2.68), diclofenac (RR 1.73; 95% CI 1.21, 2.46), piroxicam (RR 1.66; 95% CI 1.14, 2.44), tenoxicam (RR 1.43; 95% CI 0.40, 5.14), meloxicam (RR 1.24; 95% CI 0.98, 1.56) and ibuprofen (RR 1.19; 95% CI 0.93, 1.54).[183]

In an earlier, collaborative meta-analysis of cohort and case-control studies published between 1985 and 1994, use of all non-selective NSAIDs were associated with significantly increased risks of peptic ulcer complication hospitalizations relative to non-use.[190] Ibuprofen, at doses used in general practice, was associated with the lowest risk of peptic ulcer complication-related hospitalizations.[190] In a subsequent meta-analysis of cohort and case-control studies published between 1990 and 1999, however, risk of serious GI event-related hospitalizations and specialist visits was dose-dependent, and was no lower for ibuprofen compared to any other non-aspirin, non-selective NSAID when results were stratified by low to medium (RR 2.1, 95% CI 1.6, 2.7) or high dose (RR 5.5, 95% CI 3.0, 10.0) (Table 18).[184, 191] A more recent review of observational studies published through 2002 also found GI bleeding risk increased for all non-selective NSAIDs, and risk appeared related more to dose than to the specific drug evaluated.[11]

Table 18. Relative Risk (95% CI) of UGIB* for NSAIDs vs. non-use

	Hernandez-Diaz 2000[191]			Garcia-Rodriquez 2001[184]
		Dose		Overall
NSAID	Overall	Low-Medium	High	
Diclofenac	3.3 (2.8, 3.9)	3.1 (2.0, 4.7)	3.6 (2.3, 5.6)	4.6 (3.6, 5.8)
Ibuprofen	1.9 (1.6, 2.2)	2.1 (1.6, 2.7)	5.5 (3.0, 10.0)	2.5 (1.9, 3.4)
Indomethacin	4.6 (3.8, 5.5)	3.0 (2.2, 4.2)	6.5 (4.8, 8.6)	5.2 (3.2, 8.3)
Ketoprofen	4.6 (3.3, 6.4)	NR	NR	3.3 (1.9, 5.9)
Naproxen	4.0 (3.5, 4.6)	3.5 (2.8, 4.3)	5.1 (3.8, 6.9)	4.0 (2.8, 5.8)
Piroxicam	6.3 (5.5, 7.2)	5.6 (4.7, 6.7)	6.2 (4.4, 8.7)	6.2 (3.7, 10.1)
Sulindac	3.6 (2.8, 4.7)	NR	NR	NR

*Upper GI tract bleeding/perforation

Non-selective NSAIDs were also associated with an increased risk of serious GI events in more recent observational studies. Ibuprofen (Odds Ratio 1.42, 95% CI 1.27, 1.59), diclofenac (OR 1.96; 95% CI 1.78, 2.15) and naproxen (OR 2.12, 95% CI 1.73, 2.15) were all associated with increased risks of GI hemorrhage, perforation, surgery or undefined uncomplicated events relative to non-use in a case-control study of the UK General Practice Research Database.[138] Odds ratios for upper GI events resulting in hospitalization associated with NSAIDs relative to non-use ranged from 3.1 (95% CI 2.0, 4.9) for ibuprofen to 24.7 (95% CI 8.0, 77.0) for ketorolac based on data from 10 hospitals in Spain using a case-control design.[141]

Non-selective NSAIDs – CV Safety

Randomized controlled trials. Evidence regarding the comparative risk of serious CV events for non-selective NSAIDs is more limited than the evidence for selective COX-2 inhibitors. In particular, long-term clinical trials are lacking. A recent, fair-quality meta-analysis by Kearney and colleagues of 91 trials (mostly ranging from 4 to 13 weeks in duration) evaluated risks with any non-selective NSAID (33,260 person-years of exposure) compared to any COX-2 inhibitor (23,325 person-years of exposure).[129] Most of the trials evaluated naproxen (42 trials), ibuprofen (24 trials), and diclofenac (26 trials); only 7 evaluated other non-selective NSAIDs. Generalizability to usual practice could be limited because the majority of the trials evaluated higher than standard doses of NSAIDs. Much of the data regarding cardiovascular event rates were obtained by requesting unpublished data from trial sponsors. Other characteristics of this meta-analysis are discussed in more detail in the section on cardiovascular risks associated with rofecoxib.

Table 19 shows estimates of risk for different cardiovascular outcomes with COX-2 inhibitors relative to non-selective NSAIDs. Risk of myocardial infarction was similar with COX-2 inhibitors and non-naproxen NSAIDs, but about two-fold greater for COX-2 inhibitors compared to naproxen (0.6% or 99/16360 vs. 0.3% or 30/10,978, RR 2.04, 95% CI 1.41 to 2.96). This is equivalent to about one additional myocardial infarction for every 301 patients treated for one year with a COX-2 inhibitor instead of naproxen. COX-2 inhibitor use was also associated with a lower risk of stroke relative to non-naproxen NSAIDs (RR 0.62, 95% CI 0.41 to 0.95). In subgroup analyses of specific non-selective NSAIDs (ibuprofen, diclofenac, other non-selective NSAIDs), the difference in stroke risk was only observed with diclofenac, which was usually evaluated at high doses (RR 0.48, 95% CI 0.27 to 0.83). There was insufficient data to analyze the effects of lower doses on estimates of risk.

Table 19. Rate Ratios (95% CI)*: COX 2 inhibitor relative to non-selective NSAID[129]

NSAID group	Vascular events	Myocardial Infarction	Stroke	Vascular Death
Any non-selective NSAID	1.16 (0.97 to 1.38)	**1.53 (1.19 to 1.97), p=0.0009**	0.83 (0.62 to 1.12)	0.97 (0.69 to 1.35)
Any non-naproxen, non-selective NSAID	0.88 (0.69 to 1.12)	1.20 (0.85 to 1.68)	**0.62 (0.41 to 0.95), p=0.03**	0.67 (0.43 to 1.06)
Naproxen	1.57 (1.21 to 2.03)	**2.04 (1.41 to 2.96), p=0.0002**	1.10 (0.73 to 1.65)	1.47 (0.90 to 2.40)

*Rate ratios below 1 favor COX 2 inhibitors and rate ratios above 1 favor NSAIDs

Kearney and colleagues found insufficient data to directly estimate risks of non-selective NSAIDs from placebo-controlled trials. Indirect analyses (based on trials of non-selective NSAIDs versus COX-2 inhibitors and trials of COX-2 inhibitors versus placebo) suggest an increased risk of vascular events with ibuprofen (RR 1.51, 95% CI 0.96 to 2.37) and diclofenac (RR 1.63, 95% CI 1.12 to 2.37) relative to placebo, but not with naproxen (RR 0.92, 95% CI 0.67 to 1.26). However, indirect analyses should be interpreted with caution because they can give discrepant results compared to head-to-head comparisons.[192]

In December 2004, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) was suspended in part because of an "apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with those on placebo."[111] However, further details from the ADAPT trial have not yet become available.

Observational studies—naproxen. The risk of MI and other cardiovascular events associated with various non-selective NSAIDs has been evaluated in numerous observational studies. Naproxen has been the most extensively studied non-selective NSAID because of interest generated after the results of the VIGOR trial were published. In order to assess the proposed hypothesis that naproxen is protective against myocardial infarction (rather than rofecoxib causing additional myocardial infarctions), authors of a meta-analysis of randomized controlled trials of rofecoxib also analyzed 11 observational studies of naproxen (four based on the General Practice Research Database).[124] Compared with non-naproxen NSAIDs, naproxen was associated with a small cardioprotective effect (OR 0.86, 95% CI 0.75 to 0.99). The modest cardioprotective effect would not completely explain the 80% reduction in risk with naproxen compared with rofecoxib observed in the VIGOR trial. In addition, meta-regression analyses indicated that the funding source largely explained between-study heterogeneity. Specifically, Merck-funded studies of naproxen reported larger cardioprotective effects.

An FDA review of four observational studies of naproxen reporting a cardioprotective effect illustrate some difficulties in interpreting the results.[148] In a study by Rahme and colleagues, current exposure to naproxen was associated with a lower risk of acute MI compared with exposure to other NSAIDs (OR 0.79, 95% CI 0.63 to 0.99).[193] However, when the FDA reviewer re-analyzed the data to compare current exposure to naproxen to non-use of NSAIDs, naproxen was associated with a *higher* risk (OR 1.28, 95% CI 1.10 to 1.49).[148] Although the FDA re-analysis was not adjusted for confounders, examination of adjusted and unadjusted results in the paper suggests that the effects of adjusting would be minor. A study by Kimmel and colleagues found naproxen associated with a lower risk of MI compared with non-use (OR 0.48, 95% CI 0.28 to 0.82), but the results were susceptible to participation bias (about 50% of cases and controls participated) and recall bias (exposure determined by telephone interviews rather than by using pharmaceutical databases or other sources).[194] The third study, by Watson

and colleagues, reported a lower risk of thromboembolic cardiovascular events with current use of naproxen versus non-use (OR 0.61, 95% CI 0.39 to 0.94), but did not adequately control for baseline cardiovascular risk (it used an unvalidated composite measure of risk).[195] Further, when the endpoint of MI alone rather than the composite endpoint of thromboembolic cardiovascular events (which included subdural hematoma, subarachnoid hemorrhage, ischemic stroke, sudden death, or MI) was evaluated, the reduction in risk was not significant (OR 0.57, 95% CI 0.31 to 1.06). Finally, a study by Solomon and colleagues reported a lower risk of MI with use of naproxen within 6 months of an acute MI (OR 0.84, 95% CI 0.72 to 0.98).[196] However, the risk was reduced to a similar degree when the naproxen prescription had run out between 61 and 180 days earlier. Unless naproxen exerts a long-term cardioprotective effect (which is thought to be highly unlikely), these findings are suggestive of underlying selection bias—in other words, persons receiving naproxen were at lower risk for cardiovascular events, and adjustment for known confounders did not eliminate this bias.

In four other recent observational studies (not included in the Juni systematic review) evaluating cardiovascular risk, naproxen was not associated with a cardioprotective effect relative to non-use (Table 20).[143, 146, 149, 155, 160] However, naproxen was also not clearly associated with an increased risk of myocardial infarction. None of these studies received pharmaceutical industry funding. The FDA review also included two other unpublished studies (Ingenix and MediCal studies) that found no cardioprotective benefit associated with naproxen.[148]

Table 20. Risk of myocardial infarction associated with naproxen in recent observational studies not included in the Juni meta-analysis

Study	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005[146]	1.27 (1.01 to 1.60)
Levesque, 2005[143]	1.17 (0.75 to 1.84)
Johnsen, 2005[149]	1.50 (0.99 to 2.29)
Andersohn 2006[155]	1.16 (0.86 to 1.58)

Overall, the general conclusion from observational studies of a modest decrease in cardiovascular risk associated with naproxen relative to other NSAIDs appears consistent with a systematic review of RCTs.[129] On the other hand, protective cardiovascular effects of naproxen relative to non-use observed in some observational studies usually appear to be explainable by issues related to study design or analysis. More recent, high-quality observational studies are mostly consistent with a neutral cardiovascular effect of naproxen relative to non-use.

Observational studies—non-naproxen NSAIDs. Results from observational studies regarding the cardiovascular risk associated with non-naproxen, non-selective NSAIDs are mixed. Non-selective NSAIDs as a class and individual NSAIDs have not been consistently associated with increased risks. Results from recent observational studies from the COX-2 era are summarized in Table 21.

Table 21. Risk of myocardial infarction associated with non-selective, non-naproxen NSAIDs

Study	Drug	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005[146]	Ibuprofen Diclofenac Other non-selective, non-naproxen NSAIDs	1.24 (1.11 to 1.39) 1.55 (1.39 to 1.72) 1.21 (1.02 to 1.44)
Graham, 2005[160]	Non-selective, non-naproxen NSAIDs	1.13 (1.01 to 1.27)
Levesque, 2005[143]	Non-selective, non-naproxen NSAIDs	1.00 (0.73 to 1.37)
Johnsen, 2005[149]	Non-selective, non-naproxen NSAIDs	1.50 (0.99 to 2.29)
Garcia Rodriguez, 2004[185]	Ibuprofen Diclofenac Ketoprofen Piroxicam Indomethacin Other non-selective, non-naproxen NSAIDs	1.06 (0.87 to 1.29) 1.18 (0.99 to 1.40) 1.08 (0.59 to 1.96) 1.25 (0.69 to 2.25) 0.86 (0.56 to 1.32) 0.89 (0.63 to 1.25)
Mamdani, 2003[147]	Non-selective, non-naproxen NSAIDs	1.2 (0.9 to 1.4)
Ray, 2002[151]	Ibuprofen	0.91 (0.78 to 1.06)
Solomon, 2002[196]	Ibuprofen	1.02 (0.88 to 1.18)
Watson, 2002[195]	Ibuprofen Diclofenac	0.74 (0.35 to 1.55) 1.68 (1.14 to 2.49)
Andersohn, 2006[155]	Ibuprofen Diclofenac	1.00 (0.83, 1.21) 1.36 (1.17, 1.58)
Schlienger 2002[197]	Ibuprofen Diclofenac Piroxicam Ketoprofen Indomethacin Flurbiprofen	1.17 (0.87, 1.58) 1.38 (1.08, 1.77) 1.65 (0.78, 3.49) 1.39 (0.77, 2.51) 1.03 (0.58, 1.85) 2.26 (0.93, 5.46)

In April 2005, after reviewing the available observational data, the FDA issued a Public Health Advisory stating, "Long-term controlled clinical trials have not been conducted with most of these (non-selective) NSAIDs. However, the available data suggest that use of these drugs may increase CV risk. It is very difficult to draw conclusions about the relative CV risk among the COX-2 selective and non-selective NSAIDs with the data available. All sponsors of non-selective NSAIDs will be asked to conduct and submit to FDA a comprehensive review and analysis of available controlled clinical trial databases pertaining to their NSAID product(s) to which they have access to further evaluate the potential for increased CV risk."[198] The FDA also required labeling changes to both prescription and non-prescription non-selective NSAIDs warning about potential cardiovascular risks.

Aspirin. Aspirin is known to be protective against occlusive vascular events because of its irreversible antiplatelet effects. In a collaborative meta-analysis of 65 randomized controlled trials of aspirin for prophylaxis against thrombotic events, any dose of aspirin reduced the risk of vascular events by an average of 23% (standard error 2).[199] The cardioprotective effects of aspirin appeared lower (13%) in three trials evaluating doses of lower than 75 mg/day, but in trials that directly compared higher and lower doses, there were no significant differences. Again, the populations evaluated in these trials probably varied substantially from trials of

patients with arthritis.

In fact, randomized controlled trials assessing the risk of upper GI bleeding with aspirin have mainly been conducted in populations receiving aspirin as prophylaxis for thrombotic events. It is for this reason that the populations evaluated in these trials may differ on risk factors for bleeding compared to patients who take aspirin for arthritis, as well as being at higher cardiovascular risk. Randomized controlled trials[200] and observational studies generally reported that aspirin increases risk of serious GI events relative to placebo or non-use,[138, 190, 200, 201] but at a rate similar to that of other non-selective NSAIDs.[138, 189, 190] In these studies, the dose of aspirin varied widely and was generally lower (50 mg to 1500 mg daily) than the doses considered effective for analgesia and anti-inflammatory effects, and patients typically received aspirin for prolonged periods. In a good-quality meta-analysis of 24 randomized trials with nearly 66,000 participants, the risk of gastrointestinal hemorrhage was 2.47% with aspirin compared with 1.42% with placebo (OR 1.68, 95% CI 1.51 to 1.88), based on an average of 28 months therapy.[200] There was no relation between gastrointestinal hemorrhage and dose in this study. Further, modified release formulations did not attenuate the risk for bleeding. In a more recent, fair-quality meta-analysis of 31 randomized trials with over 190,000 subjects, the risk of major bleeding was 1.56% with doses <100 mg, 1.54% with 100-200 mg, and 2.29% with >200.[202] Although the difference between doses >200 and <100 was statistically significant, the absolute differences are small.

Systematic reviews of cohort and case-control studies published between 1985 and 2001 reported similar findings,[189, 190, 201] except that the most recent review found a dose-response relationship between aspirin and risk of bleeding.[189] However, aspirin was associated with upper GI bleeding even at low doses. Findings from a recent UK practice-based case-control study (9,407 cases) found that compared with non-use, aspirin was associated with an increased risk of complicated or uncomplicated adverse GI events (odds ratio 1.60, 95% CI 1.49, 1.72) similar to that of naproxen, diclofenac, and ibuprofen.[138] These findings are consistent with a systematic review of observational studies that only assessed peptic ulcer-related hospitalizations.[190]

Salsalate. Serious GI event rates (bleeding, perforation, obstruction) associated with salsalate were only reported in one cohort of long-term care residents in Indiana. The number of cases of GI-related hospitalizations associated with salsalate (1, 5.9%) after 14 months was similar to that of other selective and non-selective NSAIDs (cited in partially selective NSAID section above).[180]

Other Adverse Events Associated with Selective and Non-Selective NSAIDs

Mortality. Large clinical trials have not shown differences in mortality rates between different NSAIDs. In VIGOR, for example, mortality was 0.5% with rofecoxib versus 0.4% with naproxen,[19] and in CLASS mortality rates were 0.47%, 0.37%, and 0.45% for celecoxib, diclofenac, and ibuprofen, respectively.[94] A meta-analysis that included unpublished company clinical trial data (including CLASS) found no significant difference in rates of death in patients randomized to celecoxib compared with non-selective NSAIDs, though there were few events (0.03% or 6/18,325 in the celecoxib arms versus 0.11% or 14/12,685 in the NSAID arms).[62] In one retrospective cohort study of Saskatchewan health-services databases that followed patients from 6 months following prescription until death, nabumetone was associated with significantly lower rates of all-cause mortality compared with diclofenac (adjusted odds ratio 1.96; 95% CI

1.25, 3.07) and naproxen (adjusted odds ratio 2.95, 95% CI 1.88, 4.62).[203] However, we found no other studies replicating this finding.

Hypertension, CHF, edema, and renal function. All non-selective NSAIDs appear to be associated with increases in blood pressure. However, evidence regarding differential effects of specific NSAIDs is somewhat conflicting. Two meta-analyses of placebo-controlled trials have compared the effects of different non-selective NSAIDs on blood pressure increases.[204, 205] One meta-analysis found that non-selective NSAIDs raised mean blood pressure by an average of about 5.0 mm Hg (95% CI, 95% CI 1.2 to 8.7).[204] Piroxicam produced the most marked elevation in blood pressure.[204] By contrast, the other meta-analysis found that piroxicam and ibuprofen had negligible effects on blood pressure, and that indomethacin and naproxen were associated with the largest increases.[205] In both meta-analyses, aspirin and sulindac were associated with minimal hypertensive affect. In an analysis of head-to-head trials, there were no significant differences between indomethacin and sulindac (10 trials), indomethacin and salicylate (one trial), diclofenac and sulindac (one trial), ibuprofen and sulindac (one trial), and naproxen and sulindac (three trials).[204] The reliability of the meta-analyses is compromised by a high likelihood of publication bias; more than half of published NSAID trials did not report hypertension rates as an outcome.[205]

Several studies have reported hypertension outcomes for selective COX-2 inhibitors compared to non-selective NSAIDs. One fair-quality meta-analysis found COX-2 inhibitors as a class (celecoxib, rofecoxib, and etoricoxib) not associated with an increased risk of developing hypertension compared to non-selective NSAIDs (RR 1.25, 95% CI 0.87 to 1.78). Pooling evidence on blood pressure effects from various selective and non-selective NSAIDs may be misleading, however, because of potential differences between COX-2 inhibitors, dissimarilities in dosing and comparator drugs, and a high likelihood of publication bias affecting conclusions.

Evidence regarding risks of hypertension with rofecoxib is somewhat mixed. A good-quality Cochrane review found that rates of edema and hypertension were not reported in most trials.[77] For rofecoxib versus nabumetone, there was no difference in the rate of hypertension in two trials (pooled RR 1.46, 95% CI 0.53 to 4.12). A meta-analysis of nine phase IIb/III osteoarthritis trials sponsored by the manufacturer of rofecoxib found that rofecoxib 12.5 mg and 25 mg daily were associated with higher rates of lower extremity edema, congestive heart failure, and hypertension than placebo.[206] Edema and hypertension rates were similar between the rofecoxib (1.2 per 100 patient-months) and ibuprofen (1.3 per 100 patient-months) groups but somewhat higher than in the diclofenac group (0.3 per 100 patient months). Discontinuations due to these adverse events were rare: of 2,829 randomized to rofecoxib, seven discontinued due to edema, two due to hypertension, and one due to CHF. However, five of the nine trials were shorter than 6 weeks in duration, so these rates may not be representative of results in long-term users. A more recent fair-quality meta-analysis of arthritis trials found rofecoxib associated with a higher risk of developing hypertension compared to either placebo (RR 2.63, 95% CI 1.42 to 4.65) or non-selective NSAIDs (RR 1.78, 95% CI 1.17 to 2.69).[21]

Results of large, longer-term trials appear to be consistent with an increased risk of hypertension with rofecoxib compared to either placebo or non-selective NSAIDs. In VIGOR (N=8,076) rofecoxib 50 mg daily was associated with a higher risk of developing hypertension compared to naproxen (RR 1.69, 95% CI 1.42-1.99) and a higher risk of discontinuation due to hypertension-related adverse events (RR 4.67, 95% CI 1.93 to 11.28).[114] In addition, 19 patients developed CHF-related adverse events during 4,047 patient-years of exposure, compared with

nine patients during 4,029 patient-years of exposure to naproxen (RR 2.11, 95% CI 0.96 to 4.67). In the long-term APPROVe polyp prevention trial, hypertension (RR 2.02, 95% CI 1.71 to 2.38), edema (RR 1.57, 95% CI 1.17 to 2.10), and heart failure or pulmonary edema (RR 4.61, 95% CI 1.50 to 18.83) were all increased with rofecoxib 25 mg qD compared with placebo.[132]

In contrast to rofecoxib, several meta-analyses of celecoxib suggest no increased risk of hypertension or heart failure compared to non-selective NSAIDs. In fact, a recent fair-quality meta-analysis found celecoxib (dose not specified) not associated with an increased risk of hypertension compared to either placebo (RR 0.81, 95% CI 0.13 to 5.21) or non-selective NSAIDs (RR 0.82, 95% CI 0.68 to 1.00).[21] On the other hand, a Pfizer-funded meta-analysis submitted to the FDA found that, for celecoxib (any dose), the risk of developing hypertension was higher than placebo (1.1% vs. 0.7%, p=0.023) but lower than the non-selective NSAIDs (1.5% vs. 2.0%, p=0.002).[135] Heart failure was more frequent in patients taking celecoxib than those taking placebo (13 of 8,405 versus one of 4,057, p=0.046), though not compared with non-selective NSAIDs (0.1% vs. 0.2%, p=0.056). A third meta-analysis, funded in part by the manufacturer, reported similar findings for risk of hypertension (celecoxib vs. non-selective NSAID RR 1.1, 95% CI 0.90 to 1.3) and heart failure (celecoxib vs. non-selective NSAID RR 0.70, 95% CI 0.43 to 1.1).[62] Most of the trials included in the meta-analyses were short-term and only one meta-analysis[62] evaluated the quality of the trials. However, results from large trials of celecoxib are consistent with the meta-analyses. In CLASS (N=8,059), celecoxib was associated with a similar rate of hypertension (new-onset and aggravated pre-existing) compared with diclofenac (2.7% vs. 2.6%), but a significantly lower rate than ibuprofen (2.7% vs. 4.2%).[105] CHF rates were similar in patients randomized to celecoxib versus either ibuprofen or diclofenac (0.3% vs. 0.3%). In the shorter-term SUCCESS-I trial (N=13,274), rates of hypertension were similar with celecoxib 100 or 200 mg bid compared to either diclofenac or naproxen (RR 0.86, 95% CI 0.62 to 1.20).[21] The APC polyp prevention trial found celecoxib associated with significant systolic blood pressure elevations compared to placebo at 1 and 3 years at either 200 mg twice daily (2.0 mm Hg at 1 year and 2.6 mm Hg at 3 years) and 400 mg twice daily (2.9 mm Hg at 1 year and 5.2 mm Hg at 3 years).[109] By contrast, the PreSAP polyp prevention trial found no difference in systolic blood pressure elevations between celecoxib 400 mg once daily and placebo.[109] The APC polyp prevention trial found no difference in rates of heart failure between patients randomized to celecoxib versus those randomized to placebo, though event rates were low (five cases of heart failure among 1,356 subjects).[108]

Direct evidence on comparative blood pressure effects of celecoxib compared to rofecoxib is more limited. A good-quality Cochrane review found no difference in rates of clinically significant increases in blood pressure or edema with rofecoxib versus celecoxib in three head-to-head trials of average-risk populations with osteoarthritis.[77] Another meta-analysis that used unpublished clinical trial reports also found no difference in risk of hypertension or aggravated hypertension in patients on celecoxib versus rofecoxib (RR 0.75, 95% CI 0.52 to 1.1).[62] On the other hand, in contrast to the Cochrane review, this meta-analysis found a lower rate of edema with celecoxib versus rofecoxib (5 trials, RR 0.72, 95% CI 0.62 to 0.83). A third meta-analysis found rofecoxib associated with a greater risk of developing a clinically important elevation in systolic blood pressure (RR 1.50, 95% CI 1.00 to 2.26), though the difference was not statistically significant.[21]

Three other short-term head-to-head trials of celecoxib and rofecoxib in higher-risk populations (hypertensive, osteoarthritic patients) funded by the manufacturer of celecoxib should be interpreted cautiously because they evaluated doses (rofecoxib 25 mg daily and

celecoxib 200 mg daily) that may not provide equivalent pain relief.[84, 85, 207] Two 6-week trials of elderly (>65 years) patients with osteoarthritis and on antihypertensive therapy (SUCCESS VI and SUCCESS VII) found that rates of increased systolic blood pressure (>20 mm Hg increase and absolute value >140 mm Hg) were higher in patients randomized to rofecoxib (n=399) compared to celecoxib (n=411): 14.9% vs. 6.9% ($p<0.01$) in one trial[85] and 17% vs. 11% ($p=0.032$) in the other.[84] However, in one of these trials (SUCCESS VI),[84] there was an important baseline difference in the proportion of patients who took an ACE inhibitor for hypertension (40% for celecoxib-treated patients versus 29% for rofecoxib-treated patients, $p=0.002$). This could suggest inadequate randomization, as successful randomization is unlikely to have resulted in such a marked baseline difference. In the third trial (CRESCENT), which enrolled patients with controlled hypertension, diabetes, and osteoarthritis, the proportion that developed ambulatory hypertension (systolic blood pressure >135) was higher with rofecoxib than with celecoxib (30% vs. 16%, $p=0.05$).[207] In the CRESCENT and SUCCESS-VI trials, edema was more common in patients assigned to rofecoxib compared with those assigned to celecoxib (7.7% vs. 4.7%, $p<0.05$[207] and 9.5% vs. 4.9%, $p=0.014$[84]). Three patients on rofecoxib and two on celecoxib developed heart failure in CRESCENT compared with four versus none in SUCCESS-VI; these differences were not significant. Discontinuations due to these adverse events did not differ.

With regards to renal toxicity, there is little evidence to suggest that selective NSAIDs as a class are safer than non-selective NSAIDs. A systematic review of five small (sample size range 15 to 67), short-term (28 days or less) trials found that selective NSAIDs had similar effects on glomerular filtration rate and creatinine clearance in three trials, and were modestly superior in two.[208] The clinical effects of the modest differences observed in the latter two trials are unclear. Another meta-analysis found that celecoxib at 200 to 400 mg was not associated with a greater risk of increase in creatinine greater than 1.3 times the upper limit of normal compared to non-selective NSAIDs (RR 0.78, 95% CI 0.46 to 1.3).[62]

There is also no clear evidence suggesting that celecoxib is associated with improved renal safety compared with rofecoxib. In the CLASS trial, there was one fewer episode of edema, hypertension, or increased creatinine for every 62 patients treated with celecoxib instead of ibuprofen 800 mg tid or diclofenac 75 bid.[60] The effects of celecoxib on renal function were also reviewed in a meta-analysis of primarily unpublished data (not including CLASS) that found the overall incidence of renal adverse events similar to that of non-selective NSAIDs.[209] In VIGOR, the incidence of adverse events related to renal function (outcome not specifically defined) was similar for the rofecoxib and naproxen groups (1.2% versus 0.9%), with 0.2% discontinuing treatment in each arm because of these events.[19] A meta-analysis of manufacturer's data found rofecoxib associated with an overall incidence of elevations in serum creatinine similar to non-selective NSAIDs.[206] Discontinuations due to elevated serum creatinine were rare, and there were no cases of acute renal failure (not defined) associated with rofecoxib.

The risks of hypertension and heart failure with rofecoxib and celecoxib have also been evaluated in several good-quality observational studies. A large case-control study found that rofecoxib users were at significantly increased risk for new-onset hypertension compared with patients taking celecoxib (OR 1.6, 95% CI 1.2 to 2.1).[210] A retrospective cohort study found rofecoxib associated with an increased risk of admission for heart failure compared with NSAID–non-users (RR 1.8, 95% CI 1.5 to 2.2), though celecoxib was not (RR 1.0, 95% CI 0.8 to 1.3).[163] Rofecoxib (HR 1.27, 95% CI 1.09 to 1.49) and non-selective NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) were also associated with higher risks of death or recurrent CHF compared with

celecoxib in another study of high-risk patients following a heart-failure admission.[211] In two observational studies, use of non-selective NSAIDs was associated with heart-failure admissions (RR 1.4, 95% CI 1.0 to 1.9)[163] and newly diagnosed heart failure (adjusted RR 1.6, 95% CI 1.2 to 2.1)[212] when compared with non-use.

Hepatotoxicity. We identified one systematic review that evaluated rates of aminotransferase elevations, liver-related discontinuations, and other serious hepatic adverse events, including hospitalizations and deaths, in randomized controlled trials of rofecoxib, celecoxib, valdecoxib, meloxicam, diclofenac, naproxen, and ibuprofen in adults with osteoarthris or rheumatoid arthritis.[213] It identified 67 published articles and 65 studies accessible from the FDA archives. Diclofenac (3.55%, 95% CI 3.12% to 4.03%) and rofecoxib (1.80%, 95% CI 1.52% to 2.13%) had higher rates of aminotransferase elevations >3 times the upper limit of normal compared with placebo (0.29%; 95% CI 0.17% to 0.51%) and the other NSAIDs (all < or = 0.43%). However, only diclofenac was associated with a higher rate of liver-related discontinuations than placebo (2.17%, 95% CI 1.78% to 2.64%). Serious complications related to liver toxicity were extremely rare: only one liver-related hospitalization (among 37,671 patients) and death (among 51,942 patients) occurred in a patient on naproxen in the VIGOR trial. There was also a statistically significant difference in elevated (three times above the upper limit of normal) transaminase levels between lumiracoxib (which is chemically related to diclofenac) and naproxen or ibuprofen (HR 3.97, 95% CI 2.96, 5.32) in the large TARGET (N=18,325) trial, though these elevations were reversible upon drug discontinuation.[175]

A recent systematic review of seven population-based epidemiological studies of hepatotoxicity with NSAIDs found a similarly low risk of serious hepatic toxicity.[214] In those studies, the excess risk of liver injury associated with current NSAIDs ranged from 4.8 to 8.6/100,000 person-years of exposure compared with past use. There were zero deaths from liver injury associated with NSAIDs in over 396,392 patient-years of exposure. A recent cohort study from Italy found that nimesulide, an NSAID not available in the U.S., was associated with a higher incidence of serious liver injury compared with other NSAIDs.[215] None of the other NSAIDs, including celecoxib, were associated with an increased risk of serious liver injury. An earlier review of five population-based studies found sulindac associated with a 5-10 fold higher incidence of hepatic injury compared with other NSAIDs.[216] Diclofenac was associated with higher rates of aminotransferase elevations compared with users of other NSAIDs, but not with a higher incidence of serious liver disease.

Tolerability: Comparison of NSAIDS

Partially selective NSAIDs. Evidence is mixed regarding the relative tolerability of meloxicam (7.5 mg or 15 mg) compared to non-selective NSAIDs. The meta-analysis of meloxicam studies mentioned earlier found lower rates of any gastrointestinal event (OR 0.64; 95% CI 0.59, 0.69) and withdrawals due to GI events (OR 0.59; 95% CI 0.52, 0.67) compared with NSAIDs, but as mentioned before it included some inadequately blinded studies, which are less reliable for assessing withdrawals and attributing the cause of adverse events.[181] The double-blind trial of meloxicam 7.5, 15, and 22.5 mg and diclofenac 75 mg bid mentioned earlier[217] found no significant differences in rates of withdrawals due to adverse events or in incidence of overall and gastrointestinal tolerability.

In the nabumetone meta-analysis, the incidence of GI adverse events was significantly lower on nabumetone compared to non-selective NSAIDs (25.3% vs. 28.2%, p=.007), corresponding to

about one fewer event for every 34 patients treated with nabumetone.[187]

Numerous randomized controlled trials reported microscopic bleeding or endoscopic outcomes with etodoloca. However, we identified no randomized trials or systematic reviews assessing the clinical tolerability of etodolac relative to non-selective NSAIDs.

Non-selective NSAIDs. One Cochrane review evaluated the tolerability of different NSAIDs.[41] The only relatively consistent finding was that indomethacin was associated with higher rates of toxicity than other NSAIDs, but it was not clear if these differences were statistically significant.

Aspirin and salsalate. Five randomized trials have evaluated the efficacy or safety of aspirin or salsalate compared with non-aspirin NSAIDs in patients with arthritis.[56, 218-221] All were short-term in duration (≤ 12 weeks) and involved a total of 471 patients; of the subjects enrolled, only four had osteoarthritis of the hip/knee for every 100 patients with rheumatoid arthritis. Aspirin was associated with higher incidence of overall adverse events than salsalate (70% vs. 40%, $p<0.05$)[56] and diclofenac (61% vs. 46%; $p\leq0.05$);[218] these led to higher rates of withdrawals due to adverse events for aspirin compared with diclofenac (23% vs. 6%; $p<0.05$). Salsalate was associated with a higher incidence of overall adverse events compared to other non-selective NSAIDs in two[220, 221] of three trials, but the actual rates were not reported.

The overall safety profile of salsalate has also been evaluated in the rheumatoid arthritis population using the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) databases. These studies reported summary measures of drug toxicity based on tabulations of mean frequencies of overall adverse events per patient years, weighted by severity, and adjusted for differences in demographic factors. Numerically larger index scores indicate greater levels of toxicity. The summary index score takes into account symptoms from all body systems, laboratory abnormalities, and all-cause hospitalizations.[201, 222-224] Symptoms were assessed every 6 months using patient self-report in response to open-ended questions. Hospitalization and death data were ascertained from discharge summaries and death certificates. Descriptions of study methods varied, but in general the ARAMIS studies were somewhat vague with regard to patient selection and ascertainment methods; adverse events were not clearly defined or prespecified; exposure duration and length of follow-up were unclear; and adjustments were made only for demographic factors such as age and gender. Because the results of these studies are more subject to recall bias and had other methodological shortcomings, the findings that aspirin, salsalate, and ibuprofen were the least toxic among the NSAIDs studied (Table 22 below) are less convincing than results of more recent observational studies (discussed earlier).

Table 22. Toxicity Index Scores from ARAMIS database studies

Study	Aspirin	Ibuprofen	Salsalate	Others (range)
Fries 1991[222]	1.19	1.94	1.28	2.17 (Naproxen) to 3.99 (Indomethacin)
Fries 1993[224]	1.33	1.89	NR	1.90 (Naproxen) to 2.86 (Tolmetin)
Fries 1996[223]	1.77	2.68	2.00	1.63 (Sulindac) to 3.09 (Ketoprofen)
Singh 1997[201]	2.25	1.95	1.79	3.29 (Naproxen) to 5.14 (Meclofenamate)

COX-2 vs. NSAID. Two manufacturer-funded meta-analyses[61, 62] and one good-quality Cochrane review[225] found celecoxib consistently associated with more favorable overall and GI tolerability profiles relative to some, but not all, non-selective NSAIDs in short-term RCTs of

patients with OA/RA (Table 23). Evidence of relative tolerability is less consistent for rofecoxib compared to partially-selective or non-selective NSAIDs in short-term RCTs of patients with OA/RA as reported in one manufacturer-funded meta-analysis,[226] two good-quality Cochrane reviews;[77, 78] and one other RCT that was not included in the systematic reviews.[76]

Effect size differences between the COX-2 manufacturer-funded analyses and the Cochrane reviews may have been due, in large part, to differences in methods of study selection and statistical analyses. The Cochrane Reviews primarily relied upon electronic database searches for identification of published RCTs evaluating narrow patient populations, and results from each trial were generally presented separately.[77, 78, 225] Manufacturer-funded meta-analyses relied soley[62, 226] or in part[61] on internal records to identify studies and presented only pooled estimates of broader populations including OA and RA patients.

Table 23. Tolerability profile of COX-2's vs. NSAIDs in meta-analysis and systematic reviews

Review	AE incidence		Withdrawals	
	Overall	GI-related	Any AE	GI-related
Celecoxib vs. NSAIDs for OA/RA				
Manufacturer-funded meta-analyses				
Deeks 2002[61]	-	-	RR 0.86 (0.72, 1.04)	**RR 0.54 (0.42, 0.71)**
Moore 2005[62]	**0.96 (0.94, 0.98)**	**0.84 (0.81, 0.87)**	**RR 0.86 (0.81, 0.91)**	**RR 0.75 (0.7, 0.8)**
Celecoxib vs. individual NSAIDs for RA				
Gamer 2005a[225] *(Cochrane Collaboration Systematic Review)*				
	Celecoxib vs. Naproxen			
	-	-	No differences (RR Range: 1.02-1.36)	No differences (RR Range: 0.26-0.61)
	Celecoxib vs. Diclofenac			
	0.75 (0.62, 0.90)	0.95 (0.85, 1.04	**0.54 (0.36, 0.79)**	**0.36 (0.21, 0.60)**
Rofecoxib vs. NSAIDs for OA				
Watson 2000[226] *(Manufacturer-funded meta-analysis)*				
6-month	-	**0.86 (0.78, 0.95)**	-	**0.68 (0.50, 0.92)**
12-month	-	**0.88 (0.80, 0.97)**	-	**0.70 (0.52, 0.94)**
Gamer 2005c[77] *(Cochrane Collaboration Systematic Review)*				
	Rofecoxib vs. Diclofenac			
	No differences (RR range: 0.98-1.01)	-	**12.5 mg: 0.71 (0.52, 0.97)** **25 mg: 0.70 (0.51, 0.95)**	-
	Rofecoxib vs. Ibuprofen			
	NS (RR range: 0.98-1.04)	-	↓ risk in 2 of 3 RCTs	No differences in 3 of 4 RCTs
	Rofecoxib vs. Naproxen			
	No differences	0.55 (0.42, 0.73)	No differences	↓ risk in 2 of 3 RCTs
	Rofecoxib vs. Nabumetone			
	NR	NR	No differences	No differences
Rofecoxib vs. Naproxen in RA				
Gamer 2005b[78] *(Cochrane Collaboration Systematic Review)*				
	-	-	1.02 (0.92, 1.12)	**0.74 (0.64, 0.85)**

A manufacturer-funded meta-analysis found that tolerability of valdecoxib relative to NSAIDs appeared to be time-dependent.[227] Significant increases in overall adverse event incidence (RR 1.1; 95% CI 1.04, 1.2) and incidence of GI adverse events (RR 1.4; 95% CI 1.2, 1.6) for valdecoxib relative to NSAIDs did not lead to increased risk of discontinuation in RCTs

of 6-12 weeks' duration. By 12-26 weeks, however, valdecoxib was associated with significantly lower rates of overall adverse events (RR 0.9; 95% CI 0.85, 0.93) and GI-related adverse events (RR 0.7; 95% CI 0.7, 0.8) relative to non-selective NSAIDs, as well as lower rates of discontinuation due to any adverse event (RR 0.9; 95% CI 0.85, 0.93) and due to GI-related adverse events (RR 1.4; 95% CI 1.2, 1.6).

Comparison between COX-2 inhibitors. Incidence of and withdrawals due to overall or GI-related adverse events were similar for celecoxib and rofecoxib across a manufacturer-funded meta-analysis[62] and a good-quality Cochrane review.[77] The manufacturer-funded meta-analysis reported that rofecoxib and celecoxib were associated with similar risks of any adverse event (RR 0.97; 95% CI 0.84, 1.1), any GI-related adverse event (RR 0.87, 95% CI 0.74, 1.03), and GI-adverse event discontinuation (RR 0.7; 95% CI 0.5, 1.2) using data from five 6- to 12-week RCTs of patients with either OA or RA.[62] The Cochrane review of rofecoxib for osteoarthritis[77] found no differences for either the total number of withdrawals (RR 0.93, 95% CI 0.76 to 1.14) or the number of withdrawals due to adverse events (RR 1.03, 95% CI 0.77 to 1.39) in five trials that compared celecoxib to rofecoxib.

Acetaminophen. We identified four systematic reviews that evaluated the efficacy and safety of acetaminophen compared with NSAIDs (selective or non-selective) for osteoarthritis.[228-231] The studies generally met all criteria for good-quality systematic reviews, except that three[229-231] did not provide sufficient detail about trials that were excluded. The overall conclusion from the reviews was that NSAIDs are modestly superior to acetaminophen for general or rest pain (Table 24). For pain on motion and overall assessment of clinical response, NSAIDs also appeared modestly superior, though the differences were not always statistically significant.[229, 230]. Only two reviews assessed functional disability; neither found clear differences.[229, 230]

Table 24. Pain relief in systematic reviews of acetaminophen versus NSAID

Systematic review	Date of last search	Number of head-to-head trials included	Main results for outcome of general or rest pain
Towheed, 2005[229]	Through 8/02	5 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (SMD 0.32, 95% CI 0.08 to 0.56) and HAQ pain (SMD 0.27, 95% CI 0.05 to 0.48)
Zhang, 2004[231]	Through 7/03	8 (3 trials evaluated coxibs)	NSAIDS superior using WOMAC scale (pooled ES 0.3, 95% CI 0.17 to 0.44) and clinical response rate (RR 1.24, 95% CI 1.08 to 1.41)
Lee, 2004[228]	Through 2/03	6 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (weighted mean difference –6.33, 95% CI –9.24 to –3.41)
Wegman, 2004[230]	Through 12/01	3 (no trials evaluated coxibs)	NSAIDs superior for general/rest pain (standardized mean difference 0.33, 95% CI 0.15 to 0.51)

The risk of adverse events with acetaminophen versus NSAIDs was assessed in three systematic reviews (Table 25).[228, 229, 231] In two reviews, there were no differences in withdrawal due to any adverse event.[229, 231] However, acetaminophen was associated with fewer gastrointestinal side effects compared with non-selective NSAIDs (though not compared with coxibs)[229, 231] and fewer withdrawals due to gastrointestinal adverse events.[229]

Table 25. Adverse events in systematic reviews of acetaminophen versus NSAID

Systematic review	Withdrawal due to adverse events	GI adverse events
Towheed, 2005[229]	No difference (8% vs. 9%)	Withdrawal due to GI adverse event Naproxen or ibuprofen vs. acetaminophen: RR 2.15 (95% CI 1.05 to 4.42) Any GI adverse event Non-selective NSAID vs. acetaminophen: RR 2.24 (95% CI 1.23 to 4.08) Coxib vs. acetaminophen: RR 0.96 (95% CI 0.57 to 1.61)
Zhang, 2004[231]	Not reported	GI discomfort Non-selective NSAID vs. acetaminophen: RR 1.39 (95% CI 1.07 to 1.80) Coxib vs. acetaminophen: RR 0.65 (95% CI 0.17 to 2.52)
Lee, 2004[228]	NSAID vs. acetaminophen: OR 1.45, 95% CI 0.93 to 2.27)	Not reported

Results of recent, good-quality randomized trials (not included in any of the systematic reviews) were consistent with the systematic reviews. One two-week trial (N=222) found ibuprofen 1,200 mg/day more effective than paracetamol 3,000 mg/day for pain relief ($p<0.005$) and functional disability using WOMAC scores (-20.8 versus –13.4, $p<0.001$).[232] Two cross-over trials of identical design (N=524 and 556) found celecoxib modestly superior to acetaminophen for WOMAC scores (difference in WOMAC score improvements ranged from 2.8 to 5.0 points on a 100-point scale), visual analogue pain scales (mean difference in scores ranged from 3.5 to 7.7 mm on a 100 mm scale), and patient preferences (53% and 50% favored celecoxib, versus 24% and 32% favored acetaminophen).[233] In all three trials, tolerability and safety were equivalent.

Clinical trials of acetaminophen have not been large enough to assess serious but less common complications such as PUB, myocardial infarction, acute renal failure, or hypertension. However, observational studies provide some additional information about the safety of acetaminophen relative to NSAIDs. A good-quality nested case-control study of 1,197 cases and 10,000 controls from a population-based cohort of 458,840 persons in the General Practice Research Database found current acetaminophen use associated with a lower risk for symptomatic peptic ulcer (adjusted RR 1.9, 95% CI 1.5 to 2.3) than NSAID use (adjusted RR 4.0, 95% CI 3.2 to 5.1) when each was compared with non-use.[234] There was no clear relationship between higher acetaminophen dose and increased risk for symptomatic ulcers. An earlier analysis on the same database also found current acetaminophen use associated with a lower risk for upper gastrointestinal bleeds or perforations (adjusted RR 1.3, 95% CI 1.1 to 1.5) than current NSAID use (adjusted OR 3.9, 95% CI 3.4 to 4.6), each compared with non-use.[184] A retrospective cohort study of elderly patients found that patients using lower doses of acetaminophen (<2,600 mg/day) had lower rates of GI events (defined as GI-related hospitalizations, ulcers, and dyspepsia) compared with users of NSAIDs (RR 0.73, 95% CI 0.67 to 0.80 for 1,951 to 2,600 mg/day), but the risks were similar at higher doses (RR 0.93 to 0.98).[235] Although GI hospitalization rates were not reported separately, the authors noted that dyspepsia was responsible for most of the increase in GI events in the high-dose acetaminophen groups. A meta-analysis on individual patient data from three earlier retrospective case-control studies (2472 cases) was consistent with the above studies.[236] It found acetaminophen associated

with a minimal increase in the risk for serious upper gastrointestinal bleeding (OR 1.2, 95% CI 1.1 to 1.5). By contrast, non-selective NSAIDs were associated with higher risks, though estimates of risk varied considerably for different NSAIDs (OR 1.7 for ibuprofen to 34.9 for ketoprofen).

No randomized trial has evaluated the association between acetaminophen use and myocardial infarction or other thromboembolic cardiovascular events. However, a recent analysis from the large, prospective Nurses' Health Study found heavy use of acetaminophen (more than 22 days/month) associated with an increased risk of cardiovascular events (RR 1.35, 95% CI 1.14 to 1.59) similar to that with heavy use of NSAIDs (RR 1.44, 95% CI 1.27 to 1.65).[237] Dose- and frequency-dependent effects were both significant.

The association between renal failure and acetaminophen use has been evaluated in several case-control studies. Interpretation of these studies, however, is difficult because many had important flaws (such as failure to identify patients early enough in the course of their disease to insure that the disease had not led to a change in the use of analgesics, failure to specify diagnostic criteria, failure to adjust for the use of other analgesics, incompleteness of data on exposure, and use of proxy respondents) in the collection or analysis of data.[238] The largest (926 cases) case-control study was designed to try to avoid many of these flaws.[239] It found regular use of acetaminophen associated with an increased risk for chronic renal failure (Cr >3.8 for men and >3.2 for women) compared with non-use (OR 2.5, 95% CI 1.7 to 3.6). Use of NSAIDs was not associated with an increased risk (OR 1.0). A prospective cohort study of 1,697 women in the Nurses' Health Study found increased lifetime acetaminophen exposure associated with a higher risk of decline in glomerular filtration rate of 30% or greater ($p<0.001$), though NSAIDs were not ($p=0.88$).[240] The absolute risk of renal function decline, however, was modest, even in women reporting high amounts of lifetime acetaminophen use. Compared with women consuming less than 100 g of cumulative acetaminophen, the odds of a decline in GFR of at least 30 mL/min per 1.73 m^2 for women consuming more than 3,000 g was 2.04 (95% CI, 1.28 to 3.24). By contrast, analyses of men in the Physicians' Health Study found no association between acetaminophen or NSAIDs and change in kidney function.[241, 242]

The risk of heart failure associated with acetaminophen has not been well studied. In a single study using the General Practice Research Database, current use of acetaminophen was associated with a higher risk of newly diagnosed heart failure compared with non-use (RR 1.33, 95% CI 1.06 to 1.67), though the risk was lower compared with current use of NSAIDs (RR 1.59, 95% CI 1.23 to 2.05).[212]

The risk of hypertension has been evaluated using data from the Nurses' Health Studies[243-245] and the Physicians' Health Study.[246] In the Nurses' Health Studies, acetaminophen and NSAIDs were associated with similar increases in risk of incident hypertension (Table 26). In the Physicians' Health Study, on the other hand, there was no association between NSAID or acetaminophen use and hypertension.

Table 26. Incidence of hypertension in the Nurses' Health Study and Physicians' Health Study according to use of acetaminophen or NSAIDs

Study	Acetaminophen use versus non-use: odds ratio	NSAID use versus non-use: odds ratio
Nurses' Health Study I (women 51 to 77 years old)[243]	1.93 (1.30 to 2.88)	1.78 (1.21 to 2.61)
Nurses' Health Study II (women 34 to 53 years old)[243]	1.99 (1.39 to 2.85)	1.60 (1.10 to 2.32)
Physicians' Health Study[246]	1.08 (95% CI 0.87 to 1.34)	1.05 (95% CI 0.89 to 1.24)

Although overdoses with acetaminophen can lead to potentially life-threatening hepatotoxicity, it is not clear if hepatotoxicity is associated with therapeutic doses in patients without underlying liver disease.[16] We identified no studies comparing the incidence of hepatotoxicity with therapeutic doses of acetaminophen and NSAIDs. We also identified no studies comparing the incidence of myocardial infarctions in persons using acetaminophen compared with NSAIDs.

Glucosamine and Chondroitin

Data regarding the comparative efficacy of glucosamine versus NSAIDs in patients with osteoarthritis are mixed. The most promising results have been observed in trials sponsored by Rotta Research Laboratories (based in Europe), which manufactures pharmaceutical grade glucosamine not available in the U.S. Because the content and purity of over-the-counter glucosamine preparations vary substantially, the results of the Rotta trials may not be directly applicable in the U.S.[247]

A recently updated (searches through November 2004), good-quality Cochrane review included four short-term (4 to 8 weeks) head-to-head trials of glucosamine versus an oral NSAID (ibuprofen or piroxicam).[248] Two of the trials were rated 5 out of 5 on the Jadad scale, and the other two were rated 3 or 4 out of 5. Rotta Research Laboratories sponsored three of the trials; the fourth[249] was also conducted in Europe, but funding information was not reported. One of the trials has only been published as an abstract,[250] and analyses were based on data from an unpublished manuscript. Two of the four trials found glucosamine superior to oral NSAIDs for efficacy,[249, 250] and two found no difference.[251, 252] In pooled analyses, glucosamine was superior to an oral NSAID for improving pain (three trials, standardized mean difference –0.40, 95% CI –0.60 to –0.19), but not for improving function using the Lequesne Index (two trials, SMD –0.36, 95% CI –1.07 to 0.35). Glucosamine was also associated with fewer adverse events (RR 0.29, 95% CI 0.19 to 0.44) and withdrawals due to toxicity (RR 0.06, 95% CI 0.01 to 0.25). Two small (N=40 and N=45), 12-week Canadian trials, neither funded by Rotta Research Laboratories, have also recently been published. Neither found differences between glucosamine and ibuprofen for general osteoarthritis pain[253] or for tempomandibular joint osteoarthritis.[254] Only limited details of the study design were reported for the first trial, though the second met all criteria for a good-quality study.

Evidence regarding the efficacy of glucosamine compared with placebo has also been mixed. The Cochrane review found glucosamine no better than placebo when the analysis was restricted to the eight trials with adequate allocation concealment.[248] By contrast, when all placebo-

controlled trials were included in the analysis, glucosamine was superior for both pain and function using the Lequesne index. The benefits of glucosamine also varied substantially depending on the preparation being studied. Specifically, glucosamine performed better in the seven trials evaluating the Rotta preparation (a prescription formulation available in Europe) (SMD –1.31, 95% CI –1.99 to –0.64) compared with the eight trials using non-Rotta preparations (SMD –0.15, 95% CI –0.35 to 0.05). In fact, all of the five trials that found no benefit from glucosamine evaluated a non-Rotta brand of glucosamine and also had limited or no affiliation with a manufacturer of glucosamine. Older systematic reviews found glucosamine superior to placebo, but did not include several newer and higher quality trials that demonstrated no effect, and also noted important methodological flaws that could have exaggerated estimates of effect.[255, 256] The Cochrane review[248] and one other recent, good-quality systematic review[257] included two trials (one fair-quality and one good-quality) that found glucosamine (Rotta brand) superior to placebo for reducing progression of knee joint space narrowing over 3 years (SMD 0.24, 95% CI 0.04 to 0.43[248] and RR 0.46, 95% CI 0.28 to 0.73[257]). Other trials were too short in duration (mean 9 weeks) to assess joint space narrowing as an outcome. In all of the systematic reviews, rates of adverse events were no different between glucosamine and placebo.

We identified no trials comparing chondroitin sulfate to oral NSAIDs. Three systematic reviews evaluated the efficacy and safety of chondroitin compared with placebo. The most recent, fair-quality systematic review found indistinguishable efficacy for glucosamine and chondroitin and combined the results of the trials.[256] When all trials were pooled, active treatment was associated with an increased likelihood of being a responder (RR 1.59, 95% CI 1.39 to 1.83) compared with placebo. The results of the chondroitin trials were not reported separately. The chondroitin trials also received lower quality ratings than the glucosamine trials, but the effects of quality scores on the findings were not evaluated. Assessment of the effects of quality on assessments of estimates of benefit are important because an earlier, good-quality systematic review found pooled effect sizes for pain relief substantially lower for chondroitin trials with quality scores below the median (effect size 1.7, 95% CI 0.7 to 2.7) compared with trials with quality scores above the median (ES 0.8, 95% CI 0.6 to 1.0).[255] Smaller chondroitin trials also reported higher effects. The third systematic review was also rated fair quality because it did not evaluate the effects of study quality on results.[258] It found chondroitin superior to placebo for pain and function, but longer and larger studies were needed. All three systematic reviews found chondroitin tolerated as well as placebo, with only mild adverse events.

Results of a large (N=1,583), NIH-funded, randomized trial (Glucosamine/chondroitin Arthritis Intervention Trial) comparing placebo, celecoxib, glucosamine, chondroitin, and glucosamine plus chondroitin were recently published (Table 27).[259] Using pharmaceutical grade glucosamine hydrochloride (rather than the over-the-counter glucosamine sulfate commonly available in U.S. as supplements not regulated as pharmaceuticals by the FDA) and chondroitin under an investigational new drug application, the study randomized patients stratified according to baseline pain severity. It found no differences between glucosamine, chondroitin, or the combination relative to placebo among all patients for achieving a clinical response (>20% improvement in WOMAC Pain score after 24 weeks), though the combination was superior to placebo for achieving a clinical response in an analysis of a small (20% of enrollees) subgroup of patients with moderate to severe (WOMAC 301 to 400 mm) baseline pain (79% vs. 54.3%, p=0.002). There were no statistically significant differences between celecoxib and any of the other active treatment arms (glucosamine alone, chondroitin alone, or glucosamine plus chondroitin) or placebo and either glucosamine or chondroitin alone. The

authors postulated that lack of effect in the mild baseline pain group could have been due in part to floor effects. High placebo response rates were also observed. All of the interventions were well tolerated.

Table 27. Response rates in the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) [260]

Intervention	All patients	Moderate-severe baseline pain (WOMAC pain score 301-400 mm)	Mild baseline pain (WOMAC pain score 125-300)
Placebo	60.1%	54.3%	61.7%
Celecoxib	70.1% (p=0.008 vs. placebo)	69.4% (p=0.06 vs.placebo)	70.3% (p=0.04 vs. placebo)
Glucosamine	64.0% (p=0.30 vs. placebo)	65.7% (p=0.17 vs. placebo)	63.6% (p=0.67 vs. placebo)
Chondroitin	65.4% (p=0.17 vs. placebo)	61.4% (p=0.39 vs. placebo)	66.5% (p=0.27 vs. placebo)
Glucosamine + chondroitin	66.6% (p=0.09 vs. placebo)	79.2% (p=0.002 vs. placebo)	62.9% (p=0.80 vs. placebo)

Key Question 1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?

Duration of exposure and dose may have an influence on the benefits and harms associated with selective and non-selective NSAIDs, though data are limited and somewhat inconsistent. For rofecoxib, the VIGOR trial found that an increased risk of cardiovascular events appeared to became apparent only after 8 months of treatment.[106] Similarly, initial reports of the APPROVe trial appeared to show a duration-dependent effect, as the cardiovascular event rate curves for rofecoxib and placebo diveraged only after about 18 months.[132] However, a re-analysis that included originally censored events (occurring 14 days or more after discontinuation of study drug) suggests that the curves began to diverge after only 4 to 6 months, with no evidence of deviation from the proportional hazard over time.[133] The lack of an association with shorter duration of exposure in VIGOR could have been due in part to lack of power to detect differences due to small numbers of events. Supporting this hypothesis are two recent meta-analyses that found that risk of cardiovascular events with rofecoxib[124] or COX-2 inhibitors in general[129] did not vary according to duration of treatment. One of the meta-analyses also found that cardiovascular risk of rofecoxib did not vary according to dose.[124] However, the presence or absence of dose-dependent cardiovascular effects are difficult to analyze because 85% (84/98) of the events in patients allocated to rofecoxib in placebo-controlled trials occurred at a dose of 25 mg/day.[129]

Observational data also suggests that increased cardiovascular risk with rofecoxib may occur at lower doses[145] and with shorter-term exposure.[152, 261] Odds of acute MI were greater overall for rofecoxib relative to celecoxib in a case-control study of low-income Medicare beneficiaries

(mean age 79 years) exposed to treatment for ≤ 90 days.[145] The risk estimate for those taking rofecoxib > 25 mg (OR 1.70; 95% CI 1.07, 2.71) was greater than for those taking ≤ 25 mg (OR 1.21; 95% CI 1.01, 1.44), however.[145] Risk of CV events was similar for rofecoxib and meloxicam, regardless of duration, in a cohort study in which data was ascertained from an England National Health Services database using a Prescription Event Monitoring system.[262] In a case-control study of elderly patients in Quebec, the risk of acute myocardial infarction was highest following the first prescription of rofecoxib (adjusted RR 1.64, 95% CI 1.20 to 2.23 compared to non-use) and returned to baseline by the 8th prescription.[261]

Some studies also suggest that duration of exposure and dose could influence the cardiovascular safety of celecoxib. Celecoxib was not associated with excess cardiovascular risk when compared with diclofenac or ibuprofen in the CLASS trials[60] or in meta-analyses[105, 135] of mostly short-term trials of patients with arthritis. The long-term (33 months) APC polyp prevention trial was the first trial to clearly show an increased risk of cardiovascular events relative to placebo with celecoxib.[108] However, even though it's possible that the lack of an association in CLASS and earlier meta-analyses could be due in part to less risk with shorter duration of exposure, an alternative explanation is lack of power due to small numbers of events. Regarding dose-dependent effects, one recent meta-analysis[129] of 41 placebo-controlled trials found higher doses associated with greater cardiovascular risks relative to placebo (p=0.03), though most of the events at the highest dose (800 mg/day) came from two long-term polyp prevention trials.[108, 263]

Analysis of the CLASS data also suggests that celecoxib was more effective at reducing GI events at 6 months compared with longer duration of exposure.[60] In fact, effects on pre-defined, serious GI complications were no longer present after 12 months, though interpretation of final results is problematic because of high withdrawal rates.[97] By contrast, in VIGOR, the GI benefit of rofecoxib compared to naproxen was seen early and sustained over the duration of the trial (median 9 months).[19]

One good-quality systematic review of eight trials found that higher doses of non-selective and partially selective NSAIDs were generally associated with greater efficacy for some measures of pain relief when directly compared to lower doses.[264] Higher doses were also associated with greater withdrawals due to adverse events in two of four trials. In observational studies, the risk for GI bleeding with non-selective NSAIDs also appears to increase with higher doses.[11, 191, 236] By contrast, the risk of bleeding associated with acetaminophen was not associated with dose in one meta-analysis of three case-control studies,[236] though there was a modest dose response in another case-control study of elderly patients.[235] At low over-the-counter doses, the risk of GI hospitalizations associated with aspirin, acetaminophen, and ibuprofen were similar to background rates in patients with rheumatoid arthritis or osteoarthritis in the ARAMIS database.[265] A systematic review of observational studies found that use of aspirin and non-aspirin NSAIDs at over-the-counter doses is associated with an increased risk of GI bleeding, though the risk is lower than observed at prescription doses (approximately twofold greater risk at over-the-counter doses and sixfold or higher increases at heavy prescription levels.[11] One recent analysis of the Nurses' Health Study found that the risk of cardiovascular events was dose-related for both NSAIDs and acetaminophen.[237]

We found no studies evaluating the effects of alternative drug strategies such as intermittent dosing or drug holidays on risks and benefits of oral medication use. Although one difference between the APC trial (which found an increased risk of CV events with celecoxib) and the PreSAP trial (which reported no association) was twice-daily (APC) versus once-daily (PreSAP)

dosing, no study has directly compared such dosing strategies.[109] Furthermore, other studies of twice-daily dosing with celecoxib (such as CLASS[60] and ADAPT[111]) reported no increase in CV risk.

Key Question 2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?

Demographic Subgroups Include Age, Sex, and Race

In general, the risk of cardiovascular, cardiorenal, and gastrointestinal adverse events associated with NSAIDs increase with age.[13] In one UK population, for example, the risk of adverse gastrointestinal outcomes in patients taking selective or non-selective NSAIDs was 1.36 per 1,000 patient-years for all patients 25 years or older, but 4.03 per 1,000 patient-years in patients aged 65 or more.[138] Similarly, the risk of myocardial infarction was 1.71 per 100 person-years for all patients 25 years or older, but 4.57 per 100 person-years for those 65 or older.[146] We found no trial designed to assess whether the relative harms and benefits associated with different NSAIDs for osteoarthritis varies according to age. However, even if the relative benefits and harms associated with different drugs are consistent across age groups, the absolute effects would increase with age because of greater baseline CV and GI risk.

Studies that evaluated the efficacy and safety of selective and non-selective NSAIDs in average-risk elderly patients have generally reported similar findings compared with studies in populations with younger adults. An individual patient data meta-analysis of three celecoxib trials, for example, found effects of celecoxib 200 mg/day or 400 mg/day and naproxen 1,000 mg/day similar in elderly patients when evaluating WOMAC and SF-36 scores.[266] For the SF-36, there were no statistically significant differences: naproxen scored better than celecoxib 200 mg on four of 10 components of the SF-36, while celecoxib 200 mg scored better on six, including general health. Celecoxib 200 mg was significantly better than placebo on nine of the 10 components, while naproxen was significantly better than placebo on seven. The study also confirmed that the overall incidence of GI adverse events was lower with celecoxib; the difference was about one event in 20 patients for celecoxib 200 mg and one in 10 for celecoxib 400 mg. Similarly, a meta-analysis of three rofecoxib trials reported similarly consistent efficacy for rofecoxib 12.5 mg or 25 mg daily compared to placebo among various subgroups defined by age, gender, race, location of osteoarthritis, baseline symptoms, and baseline functional status.[267] Another meta-analysis found that trials of NSAIDs in patients over the age of 60 reported similar risks for GI complications compared to trials of patients under the age of 60.[183]

Data suggesting differential effects of oral medications for osteoarthritis according to gender, ethnicity, or race are scant. In most of the published trials, a majority of subjects were women. As noted in the discussion of acetaminophen, results from the Nurses' Health Studies suggest that acetaminophen is associated with modest reductions in renal function in women,[243] but results from the Physicians' Health Study have found no association between acetaminophen use and renal dysfunction in men.[246] The effects of different NSAIDs in specific ethnic minorities have only been evaluated in small studies. In a randomized crossover study of 25 black and

Hispanic patients on ACE inhibitors, peak increases in blood pressure were similar in patients on diclofenac compared with celecoxib.[268] An observational study of 120 Native American patients seen in an Indian Health Service clinic in Phoenix who were switched to rofecoxib found that mean systolic blood pressure increased by 2.9 mm Hg overall (p=0.015) and by 4.8 mm Hg (p=0.009) in hypertensive patients.[269] We did not find any other publications focusing on the differential efficacy or safety of coxibs in African-Americans, Hispanics, or other ethnic minorities.

Co-Existing Diseases Include History of Previous Bleeding Ulcer Due to NSAIDs; Hypertension, Edema, Ischemic Heart Disease, and Heart Failure.

Rates of recurrent ulcer bleeding were similar for celecoxib 200 mg and the combinations of extended-release diclofenac 75 mg BID plus omeprazole 20 mg QD[270] or naproxen 250 mg TID plus lansoprazole 30 mg QD[271] in two fair-quality, 24-week, parallel trials involving a total of 529 patients who presented with a bleeding ulcer (Table 28). There were also no differences between celecoxib and either combination therapy in other adverse events including GI, renal, and cardiovascular symptoms or in rates of withdrawals due to adverse events. One exception was that celecoxib 200 mg QD was associated with a higher rate of dyspepsia than naproxen 250 mg TID plus lansoprazole 30 mg QD.[271] The high rates of recurrent bleeding in both the celecoxib-treated patients and in the combination therapy groups—over 10 times as high as the rate in the CLASS trial— suggest that NSAIDs and coxibs should be used with caution, if at all, in patients who have a recent history of a bleeding ulcer.

Table 28. Celecoxib in patients with bleeding ulcer history

Study Sample Size	Treatments	Recurrent ulcer bleeding at 6 months (difference; 95% CI)	Other adverse events	Withdrawals due to adverse events
Chan 2002[270] n=287	Celecoxib 200 mg BID Diclofenac 75 mg BID plus omeprazole 20 mg QD	4.9% vs. 6.3% (–1.5%, CI –6.8, 3.8%; NS)	No differences	13.3% vs. 11.9%, NS*
Lai 2005[271] ** n=242	Celecoxib 200 mg QD Naproxen 250 mg TID plus lansoprazole 30 mg QD	3.7% vs. 6.3% (-2.6; CI –9.1, 3.7; NS)	No differences for all but dyspepsia: 15% vs. 5.7%, p=0.02	10% vs. 7.4%, NS

*Includes withdrawals due to lack of efficacy
**Open trial

We found no randomized controlled trial evaluating the risk of bleeding with rofecoxib compared with celecoxib in high-risk patients. A Danish population-based case-control study of high-risk patients with previous gastrointestinal diseases found that rofecoxib (OR 2.1, 95% CI 1.2 to 3.5) and non-selective NSAIDs (OR 3.3, 95% CI 2.4 to 4.4), but not celecoxib (OR 1.3, 95% CI 0.7 to 2.8),[272] were associated with higher risks of upper gastrointestinal bleeding.

We found no randomized trials designed to assess whether the relative harms and benefits associated with different oral treatments for osteoarthritis vary according to underlying cardiovascular or renal risk. One recent analysis of three large polyp prevention trials of celecoxib or rofecoxib [109, 132] and one observational study of rofecoxib[273] found consistent risks for cardiovascular events among users at low and high baseline cardiovascular risk. However,

even if the relative risk of cardiovascular harms is consistent across risk groups, the absolute effects with any specific drug would be greater in patients at higher baseline risk. This is strikingly illustrated by a recent, good-quality population-based study of a very high risk group of 58,000 Danish patients with previous myocardial infarction that found hazard ratios for death of 2.80 (95% CI 2.41 to 3.25) for rofecoxib, 2.57 (95% CI 2.15 to 3.08) for celecoxib, 1.50 (95% CI 1.36 to 1.67) for ibuprofen, 2.40 (95% CI 2.09 to 2.80) for diclofenac, and 1.29 (95% CI 1.16 to 1.43) for other NSAIDs compared to non-use of NSAIDs.[274] Because of high rates of death in this population (95 per 1000 person-years in those not using NSAIDs), the estimated number of patients needed to treat with an NSAID for one year to cause one additional death was very low, at 13 (95% CI 10-20) for rofecoxib, 14 (95% CI 10-24) for celecoxib, 45 (95% CI 29-102) for ibuprofen, and 24 (95% CI 16-45) for diclofenac.

Only a few trials have evaluated the effects of different medications on cardiovascular and cardiorenal events specifically in high-risk patients. Three randomized trials sponsored by the manufacturer of celecoxib found higher rates of hypertension or blood pressure increases in patients randomized to rofecoxib compared with patients randomized to celecoxib, but no differences in discontinuations due to adverse events or for episodes of heart failure.[84, 85, 207] As noted earlier, the results of these trials must be interpreted cautiously because they evaluated possibly non-equivalent doses of rofecoxib and celecoxib, and because one of the trials[84] had important baseline differences suggesting inadequate randomization.

A meta-analysis funded by the manufacturer of rofecoxib found that in a high-risk subgroup of patients in whom aspirin was indicated (history of cardiovascular disease), rofecoxib was not associated with an increased risk of myocardial infarction compared with either placebo or non-selective NSAIDs.[123] However, the duration of the included trials may have been too short (median 3½ months) to detect an increased risk, few events were observed, and only a minority of patients received the high dose of rofecoxib evaluated in the VIGOR trial.

We found no trials evaluating comparative risks of different oral medications in patients with known congestive heart failure. A recent, good-quality population based retrospective cohort study, however, found that the risk of death and recurrent congestive heart failure was higher in patients prescribed NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) or rofecoxib (HR 1.27, 95% CI 1.09 to 1.49), each compared with those prescribed celecoxib.[211] We also found no trials comparing the risks and benefits of different oral medications in patients with known renal failure.

Concomitant Anticoagulant or Aspirin Use

Concomitant anticoagulants. Concomitant use of anticoagulants and non-selective NSAIDs increases the risk of GI bleeding three- to six-fold compared to anticoagulants alone.[275, 276] Several observational studies have evaluated whether COX-2 selective agents are associated with a lower risk for bleeding compared with non-selective agents in patients on anticoagulation.

A good-quality nested case-control study of elderly (>66 years old) patients on warfarin in Ontario, Canada, evaluated the association between hospitalization for upper gastrointestinal bleeding (361 cases) and use of selective or non-selective NSAIDs.[277] It found that after adjustment for potential confounders (antiplatelet agents, hypoglycemic agents, glucocorticoids, gastroprotective agents, history of previous bleed, and comorbidities), recent use of non-selective NSAIDs (OR 1.9, 95% CI 1.4 to 3.7), celecoxib (1.7, 95% CI 1.2 to 3.6), and rofecoxib (2.4, 95% CI 1.7 to 3.6) were all associated with increased and overlapping risks for upper gastrointestinal bleeding, compared with non-use. Because this study relied on pharmaceutical

databases to identify exposures prior to hospitalization, it could not assess the confounding effects of over-the-counter use of aspirin, other NSAIDs, or acid suppressive medications. It also was unable to control for variations in INR level and the risk for bleeding.

A smaller, fair-quality nested case-control study of patients in the Netherlands evaluated the risk of bleeding in anticoagulated patients receiving partially selective (meloxicam or nabumetone) COX-2 inhibitors or non-selective NSAIDs.[278] No case (N=154) received either celecoxib or rofecoxib. This study also differed from the Ontario study in that it included all cases of minor visible bleeding, hematoma, or black tarry stools. It used a questionnaire to assess exposure status and comorbidities. Patients were interviewed over the phone if answers were incomplete or unclear. The response rates were significantly higher in the cases (approximately 70%) compared with controls (approximately 31%). The study found that non-selective NSAIDs were associated with an increased risk of bleeding compared with partially selective NSAIDs after adjustment for duration of use and INR level (OR 3.07, 95% CI 1.18 to 8.03).

An open, crossover trial compared celecoxib 200 mg and rofecoxib 25 mg in 18 patients with OA, RA, or chronic pain who were stable (three consecutive INRs within 15% of each other) on warfarin therapy.[279] The trial was designed to measure mean change in INR and safety parameters. Similar rates of edema, heart failure and other adverse events were found for celecoxib and rofecoxib. The INR increased by 5% to 15% between weeks one and three for both coxibs. Four minor bleeds were reported; none were associated with a significant decrease in hemoglobin concentration.

Postmarketing case reports of serious bleeding events, some fatal, have also been reported with concomitant anticoagulation and both rofecoxib and celecoxib. Most of these events occurred in elderly patients.[135, 280]

We found no studies evaluating risks and benefits of concomitant anticoagulants and aspirin in patients with arthritis. Combination therapy has been studied in patients with indications for thromboembolic prophylaxis. However, the results of those studies are not directly applicable to patients with arthritis because of important differences in the populations (particularly with regard to cardiovascular risk), and because aspirin was used in lower, prophylactic doses (rather than anti-inflammatory and analgesic doses). One fair-quality meta-analysis (did not evaluate quality of included trials) found major bleeding risk increased with warfarin plus aspirin versus warfarin alone (at the same intensity) in patients with mechanical heart valves (3 trials, RR 1.58, 95% CI 1.02 to 2.44).[281] In patients with recent myocardial infarction or atrial fibrillation (one trial each), the increase in risk was not statistically significant (RR 3.07, 95% CI 0.33 to 28.38 and RR 2.13, 95% CI 0.20 to 23.03, respectively). In patients with mechanical heart valves, the increase in bleeding risk was offset by a reduction in thromboembolic events (RR 0.33, 95% CI 0.19 to 0.58), and there was no difference in all-cause mortality (RR 0.78, 95% CI 0.29 to 1.83). Other evidence on the risks and benefits of combination therapy has focused on comparing warfarin plus aspirin to aspirin alone. A recent good-quality meta-analysis of 10 trials, for example, found that the combination of warfarin plus aspirin increased the risk of major bleeding compared with aspirin alone following myocardial infarction or the acute coronary syndrome (RR 2.5, 95% CI 1.7 to 3.7).[282] However, the increase in bleeding risk was offset by lower risks for myocardial infarction, ischemic stroke, and revascularization. Mortality did not differ.

No study evaluated risk of bleeding in anticoagulated patients on acetaminophen compared with those on NSAIDs. A small, randomized controlled trial found acetaminophen associated with greater increases in INR levels compared with placebo.[283] Several observational studies

have also found an association between excess anticoagulation and use of acetaminophen.[284, 285] However, changes in INR are not the only important factor for predicting increased risk of bleeding. NSAIDs, for example, also affect platelet function and disrupt the gastric mucosal lining. Studies evaluating actual bleeding complications are necessary to better assess the comparative risks from acetaminophen and other NSAIDs.

No studies evaluated risk of bleeding in anticoagulated patients on glucosamine, chondroitin, or topical agents.

Concomitant aspirin. Beneficial effects of COX-2 selective inhibition on GI complication rates may be attenuated or eliminated by the concomitant use of aspirin. In the 20 per cent of patients in the CLASS trial who took aspirin in addition to their study drug, there was no difference in ulcer complications or ulcer complications plus symptomatic ulcers in patients randomized to celecoxib versus those randomized to diclofenac, ibuprofen, or the two NSAID comparators combined.[96] Similarly, a meta-analysis of randomized controlled trials found that beneficial effects of celecoxib on risk of endoscopically detected ulcers were reduced in patients on prophylactic aspirin (RR 0.49, 95% CI 0.28 to 0.86) compared with those not on aspirin (RR 0.27, 95% CI 0.16 to 0.48).[61] This analysis excluded the results of the CLASS trials because they did not evaluate endoscopic ulcers as an outcome and because of high, differential withdrawal rates. A re-analysis that included the full CLASS trials results found no benefit (rather than a reduced benefit) from celecoxib in patients on aspirin (RR 0.96, 95% CI 0.63 to 1.46),[286] but the appropriateness of combining data from trials reporting endoscopic ulcers with data from the CLASS trials on withdrawal rates, symptomatic ulcers, and ulcer complications, is disputed.[287] Another meta-analysis found that use of aspirin increased the rate of endoscopic ulcers by about 6% in patients randomized to celecoxib (4.2% without aspirin and 9.9% with aspirin) and in those randomized to a non-selective NSAID (17.6% and 23.8%).[62] In the TARGET trial, no reduction in ulcer complications with lumiracoxib compared to non-selective NSAIDs was observed in the subgroup of patients on aspirin (HR 0.79, 95% CI 0.40, 1.55).[175]

There is less evidence on the effects of aspirin on the GI risk associated with rofecoxib. A recent trial that randomized osteoarthritis patients to placebo, enteric-coated aspirin (81 mg/day), rofecoxib 25 mg/day + aspirin 81 mg/day, or ibuprofen 2,400 mg/day found similar rates of endoscopic ulcers in the rofecoxib + aspirin arm (16.1%) and the ibuprofen alone arm (17.1%); both rates were significantly higher than the placebo (5.8%) and aspirin alone (7.3%) arms.[288] A meta-analysis of aspirin users in two trials comparing celecoxib 200 mg daily and rofecoxib 25 mg daily found celecoxib associated with a lower rate of withdrawals due to GI adverse events than rofecoxib (0.7% vs. 3.9%, $p<0.05$), as well as with GI symptoms.[289] However, there were no reported serious GI events. Interpretation of these results is limited by nonequivalent dosing of the COX-2 inhibitors, pooling of data across trials, and post-hoc subgroup analyses of the aspirin-users data.

Concomitant aspirin use has not been shown to eliminate or reduce excess cardiovascular risks associated with COX-2 inhibitors. In large polyp prevention trials of rofecoxib[132] and celecoxib,[109] use or non-use of low-dose aspirin did not affect the observed increased risk of thrombotic events.[132] A recent meta-analysis of 84 placebo-controlled trials that permitted aspirin (including the polyp prevention trials) found a very similar risk of vascular events among those using aspirin (RR 1.57, 95% CI 0.90 to 2.72) and aspirin non-users (RR 1.51, 95% CI 1.14 to 2.01), though the absolute rate of events was higher in aspirin users (1.9%/year versus 1.1%/year).[129] Consistent with these findings, two large observational studies using the UK

GPRD[185] and QRESEARCH[146] databases found no significant interaction between concurrent NSAID and aspirin use and the risk of myocardial infarction. One observational study found that in patients with known cardiovascular disease, there was a higher rate of overall mortality (adjusted hazard ratio 1.93, 95% CI 1.30 to 2.87) and cardiovascular death among users of ibuprofen plus aspirin compared with users of aspirin alone, suggesting that ibuprofen (or other NSAIDs) could interfere with the cardioprotective effects of aspirin.[290] However, this study only evaluated small numbers of patients on NSAIDs, and did not adjust for important comorbidities.

Key Question 3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?

Misoprostol, standard- and double-dose H2 blockers and PPIs were all effective in reducing the risk of NSAID-associated endoscopic gastric and duodenal ulcers relative to placebo in three good-quality systematic reviews (Table 29)[291-293] of numerous randomized controlled trials of OA/RA patients.[9, 69, 291, 294-321] H2 blockers,[320-330] misoprostol (RR 0.36, 95% CI 0.20 to 0.67), and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers, but not serious cardiovascular or renal illness or death.[293]

Misoprostol has been studied most extensively and is the only agent proven to decrease risk of ulcer complications (MUCOSA).[317] In a large, good-quality trial, misoprostol was associated with a rate of definite ulcer complications of 25/4404 (0.6%) compared to 44/4439 (0.9%) with placebo (p=0.049).[317] However, misoprostol is also the only agent to be associated with a significant risk of treatment withdrawal due to nausea (RR=1.30, 95% CI 1.08 to 1.55), diarrhea (RR=2.40, 95% CI: 2.05 to 2.81), and abdominal pain (RR=1.36, 95% CI 1.20 to 1.55.

Table 29. Placebo-controlled trials of gastroprotective agents[291-293]

Treatment	# PCT studies Duration	Prevention of endoscopic ulcers		Prevention of clinical GI events*
		Gastric	Duodenal	
Misoprostol	1-1.5 months: 8 ≥ 3 months: 11	1-1.5 months: RR=0.17, 95% CI: 0.09 to 0.31 3 months: RR=0.26; 95% CI 0.17 to 0.39	1-1.5 months: RR=0.28; 95% CI 0.09-0.31 3 months: RR=0.47, 95% CI 0.33 to 0.69	Silverstein 1995 (MUCOSA): OR 0.598; 95% CI 0.364 to 0.982
H2 blockers	**Standard doses (150 mg):** 7 **Double doses (300 mg):** 3 1-3 months	**Standard dose:** insignificant effect **Double dose:** RR=0.44, 95% CI: 0.026 to 0.74	**Standard dose at 1 and 3 months:** RR=0.24, 95% CI: 0.10 to 0.57 and RR=0.36, 95% CI: 0.18 to 0.74 **Double dose:** 0.26, 95% CI 0.11 to 0.65	None
PPIs	4 Duration NR	RR=0.40, 95% CI 0.32 to 0.51	RR 0.19, 95% CI 0.09 to 0.37	None

*Upper GI hemorrhage, perforation, pyloric obstruction, death)

Table 30 reflects the results from five trials[306, 309, 314, 319, 321] that directly compare one gastroprotective agent with another, as reported in the Canadian Coordinating Office for Health Technology Assessment review.[292] Both misoprostol and omeprazole were superior to ranitidine for the prevention of gastric ulcers. Omeprazole and lansoprazole also appeared superior to misoprostol and ranitidine for the prevention of duodenal ulcers.

Table 30. Head-to-head trials of gastroprotective agents[292]

Comparison	Reductions in ulcer risk Gastric	Duodenal
Misoprostol vs. ranitidine* (2 trials; n=600)	RR=0.12 95% CI 0.03 to 0.89	No differences
Omeprazole 20 mg vs. ranitidine 150 mg (1 trial, n=425)	RR=0.32 95% CI 0.17 to 0.62	RR=0.11 95% CI 0.01 to 0.89
PPI** vs. misoprostol***	No differences	RR=0.29 95% CI 0.15 to 0.56

*standard dose
**omeprazole or lansoprazole
***secondary prophylaxis trials

A good-quality meta-analysis of 26 trials found co-administration of a PPI with a non-selective NSAID associated with a greater reduction in dyspepsia, epigrastric pain and nausea than a selective COX-2 inhibitor alone, when each was compared to a non-selective NSAID alone (relative risk reduction 66% and absolute risk reduction 9% for the PPI + non-selective NSAID versus RRR 12% and ARR 3.7% with COX-2 inhibitor).[331]

Key Question 4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations?

Topical NSAIDs - Efficacy

Four trials directly compared topical and oral NSAIDs for osteoarthritis. Two recent good-quality systematic reviews[332, 333] included three[334-336] of these trials (an older systematic review was excluded because its results appear outdated.[337]). One systematic review (by Lin et al[332]) only included osteoarthritis trials, while the other systematic review (by Mason et al[333]) included osteoarthritis and other chronic pain conditions. The systematic reviews also used different methods for abstracting and pooling efficacy data. Specifically, the primary outcome in Mason et al was a dichotomous outcome: the proportion of patients with clinical success (defined as approximately a 50% reduction in pain) at the end of the trial. By contrast, the primary outcome used by Lin et al was continuous: the difference in standardized effect sizes for the outcomes of pain, function, or stiffness measured at the end of each week of treatment. Two[335, 336] of the trials received 5 out of 5 points on the Jadad quality scale; the third[334] received a score of 3.[333] Mason et al found topical and oral NSAIDs equivalent for clinical success after 3 to 4 weeks

(pooled relative risk 1.1; 95% CI 0.9 to 1.3).[333] Although Lin et al found topical NSAIDs inferior to oral NSAIDs for pain and function after one week of treatment, this finding was based on data from only one RCT (effect size –0.38 for pain, 95% CI –0.66 to –0.10 and ES –0.32 for function, 95% CI –0.60 to –0.04).[332] There were no significant differences between topical and oral NSAIDs after 2 (one RCT), 3 (two RCTs) or 4 (one RCT) weeks. Effect sizes could not be calculated for one of the three RCTs.[334]

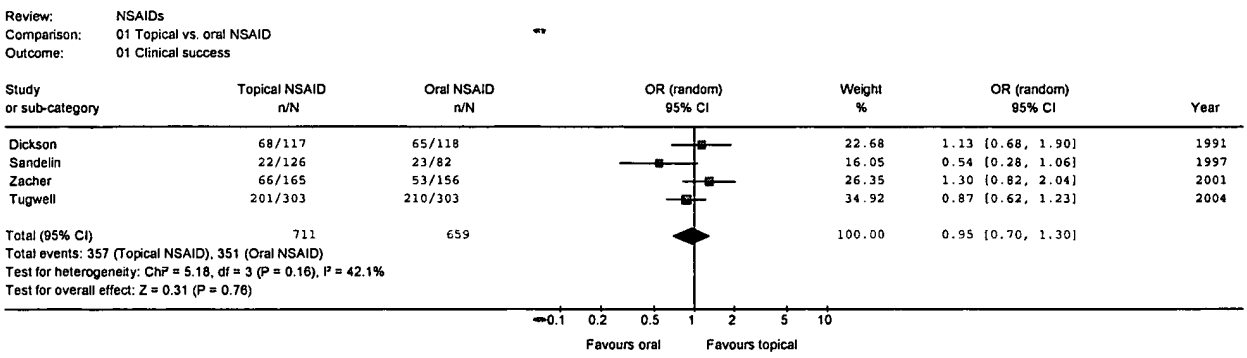
The largest and longest trial (by Tugwell et al) comparing topical and oral NSAIDs was published in 2004—too late to be included in the systematic reviews.[338] This good-quality study found the proportion of responders (as defined by Outcomes Measures in Arthritis Clinical Trials and the Osteoarthritis Research Society VI recommendations) at 12 weeks similar in patients randomized to topical or oral diclofenac (66% vs. 70%, p=0.37). There were also no clinically relevant differences for the outcomes of mean change in pain scores, physical function, or patient global assessment. The topical diclofenac evaluated in this trial was a proprietary formulation with DMSO (a drug not approved for topical use in humans by the FDA) not available in the U.S.

We pooled rates of clinical response from the four trials (including Tugwell et al) comparing topical and oral NSAIDs, using intention-to-treat (missing values=failure) results and methods similar to the Mason meta-analysis. We found no differences between topical and oral NSAIDs (OR=0.95, 95% CI 0.70-1.30). It should be noted that the Sandelin study, which reported the lowest efficacy for topical versus oral NSAIDs, evaluated topical eltenac, a drug that is no longer being investigated for use in humans.[335]

Table 31. Head-to-head trials of topical versus oral NSAID for osteoarthritis

Author, year	Condition Number enrolled	Comparison	Duration of study	Definition of clinical success
Dickson, 1991 [334]	OA of knee 235	Piroxicam 0.5% Ibuprofen 400 mg po tid	4 weeks	Patient global assessment 'good' or 'excellent'
Sandelin, 1997 [335]	OA of knee 208	Eltenac 1% gel Diclofenac 50 mg bid	4 weeks	Physician global assessment 'good'
Zacher, 2001 [336]	OA of fingers 321	Diclofenac 1% gel Ibuprofen 400 mg po tid	3 weeks	>=40% improvement in pain on 100 mm VAS
Tugwell, 2004[338]	OA of knee 622	Diclofenac 1.5% in carrier with 45.5% DMSO Diclofenac 50 mg po tid	12 weeks	OMERACT VI criteria[38] for clinical responder

Figure 1. Clinical success in trials comparing a topical versus an oral NSAID



Only three small (sample sizes 40, 85, and 129), short-term (2- to 4-week) trials directly compared different topical NSAIDs for chronic pain conditions. They found no differences between topical diclofenac and indomethacin,[339] topical flurbiprofen and piketoprofen,[340] or topical ketoprofen and diclofenac.[341]

The two systematic reviews came to somewhat different conclusions regarding the efficacy of topical NSAIDs compared with placebo. Lin et al found that topical NSAIDs were effective only during the first 2 weeks of treatment.[332] However, their conclusions at 3 and 4 weeks were entirely based on three trials that evaluated eltenac gel (no longer produced or studied for human use) or a topical salicylate (no longer classified as a topical NSAID). Mason et al, on the other hand, found NSAIDs superior to placebo (relative risk for improvement in symptoms 1.9, 95% CI 1.7 to 2.2) from 14 placebo-controlled trials of varying duration, with a number needed to treat for one case of clinical success (approximate 50% reduction in pain) of 4.6 (95% CI 3.8 to 5.9).[333] Results were not sensitive to quality ratings, trial sample size, outcome measured, or condition (knee osteoarthritis versus other musculoskeletal conditions).

Four placebo-controlled trials of topical NSAIDs for osteoarthritis[342-345] have been published since the systematic reviews were conducted. Three of these trials lasted longer than 4 weeks, and all found topical NSAIDs effective. The results of these trials are summarized in Table 32 for the dichotomous outcome "clinical success." The longest trial of topical versus oral NSAIDs—a 2-year study of topical versus oral ibuprofen funded by the UK Health Technology Assessment Program—will not be completed until 2007.[346]

Table 32. Clinical success rates in recent placebo-controlled trials of topical NSAIDs

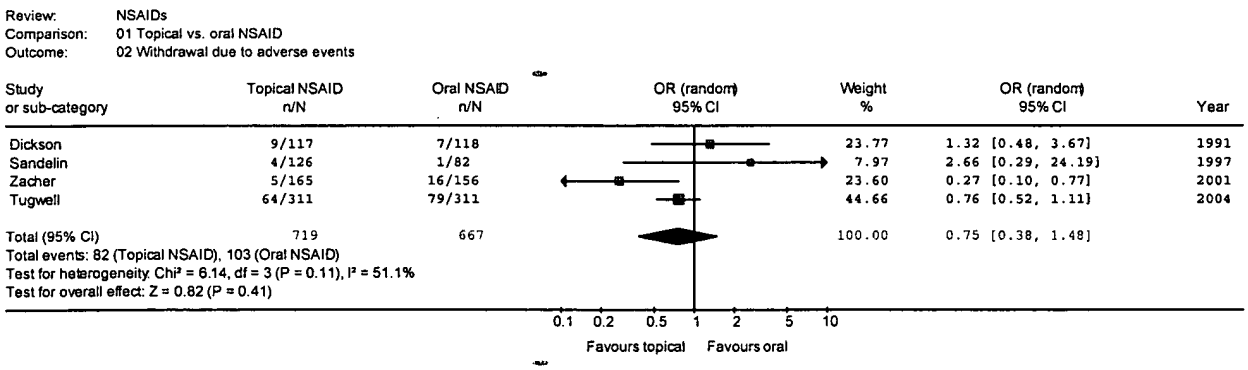
Study	Duration	Definition of 'clinical success'	Treatment group	Proportion of subjects classified as 'clinical success' at end of study period
Bookman, 2004[343]	4 weeks	>50% reduction in pain	Diclofenac Vehicle-control Placebo	44/84 (52.4%) 26/79 (32.9%) 28/84 (33.3%)
Roth, 2004[344]	12 weeks	>50% reduction in pain	Diclofenac Vehicle-control	79/163 (48.5%) 55/159 (34.6%)
Baer, 2005[342]	6 weeks	>50% reduction in pain	Diclofenac Vehicle-control	46/105 (43.8%) 27/107 (25.2%)
Trnavsky, 2004[345]	7 days	Reduction of >18 mm in VAS or >23% from baseline for pain	Ibuprofen Placebo	21/25 (84.0%) 10/25 (40.0%)

Placebo-controlled trials also suggest that topical NSAIDs differ with regard to efficacy. Topical diclofenac, which has been evaluated in the most (eight) trials, was consistently superior to placebo or associated with a trend towards superiority.[333, 342-344] Several of these trials evaluated a proprietary compound (not available in the U.S.) of topical diclofenac in a carrier containing DMSO (Pennsaid®).[347] Ibuprofen was superior to placebo for chronic pain conditions in three RCTs.[333, 345] By contrast, evidence regarding the efficacy of other topical NSAIDs for chronic conditions is much more scant (see Mason,[333] Additional Files 4 and 5). Four trials found topical piroxicam no better than placebo, homeopathic gel, or glyceryl trinitrate 1% cream. One RCT found topical ketoprofen no better than placebo. Topical felbinac, flufenamate, and indomethacin have only been evaluated in one or two small trials each. Evidence on topical flurbiprofen was mixed: one trial found topical flurbiprofen superior to placebo, but another found no differences.

Topical NSAIDs – Safety

Topical NSAIDs were associated with increased local adverse events (skin reactions such as rash, itch, and burning) compared with oral NSAIDs in two recent systematic reviews.[332, 333] However, there were no differences for total adverse events, systemic adverse events, withdrawal due to adverse events, gastrointestinal events, or central nervous system events. For the outcome of withdrawal due to adverse events, we found no differences when we pooled the three trials included in the earlier reviews and a fourth,[338] more recent trial.

Figure 2. Withdrawal due to adverse events in trials comparing a topical to an oral NSAID



Among the head-to-head trials, Tugwell et al provides the most information about adverse events because it has the largest sample size, the longest duration of follow-up, and used pre-specified definitions for adverse events and adverse-event severity.[338] Topical diclofenac was associated with more local skin reactions but with fewer systemic and laboratory adverse events (Table 33).

Table 33. Adverse events from a trial comparing topical to oral diclofenac[338]

Adverse event	Topical diclofenac in DMSO carrier (n=311)	Oral diclofenac (n=311)	P value for difference
Withdrawal due to adverse event	21%	25%	0.15
Increase in mean blood pressure >= 5 mm Hg	24%	28%	0.30
Dry skin	27%	1%	<0.0001
Rash	12%	2%	<0.0001
Pruritus	6%	0.6%	<0.0001
Gastrointestinal events (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, melena, nausea, vomiting)	35%	48%	0.0006
Severe gastrointestinal event (defined as producing significant impairment of functioning and definite hazard to patient's health)	2.6%	10.2%	0.0003
Melena	1%	2%	0.36
Asthma	3%	0.6%	0.02
Dizziness	0.6%	4%	0.002
Dyspnea	0%	2%	0.01
Hemoglobin went from normal to abnormal	2%	10%	<0.0001
Alanine transaminase increase to >3 times the upper limit or normal	1.1%	4.7%	0.01
Creatinine clearance went from normal to abnormal	4%	10%	0.01

No RCT was adequately designed to assess risks for serious but uncommon adverse events such as myocardial infarction, renal failure, or gastrointestinal bleeding. We identified one case-control study (1,103 cases) that evaluated the risk of hospital admission for upper gastrointestinal bleeding and perforation in patients taking topical NSAIDs.[348] After adjusting for the confounding effects of exposure to oral NSAIDs and ulcer healing drugs, there was no association between exposure to topical NSAIDs within 45 days of an upper GI bleed (OR 1.45, 95% CI 0.84 to 2.50 with community controls and OR 1.06, 95% CI 0.60 to 1.88 with hospital controls). By contrast, oral NSAIDs were associated with increased risk (OR 2.59, 95% CI 2.12 to 3.16 for community controls and 2.00, 95% CI 1.60 to 2.50 for hospital controls). In a nested case-control study of the General Practice Research Database, topical NSAID use was not associated with symptomatic peptic ulcer (RR=1.0 versus non-use, 95% CI 0.6 to 1.7), though oral NSAID use was associated with increased risk (RR=4.0, 95% CI 3.2 to 5.1).[234]

We identified one case-control study of similar design that found exposure to topical NSAIDs not associated with acute renal failure (adjusted OR 1.33, 95% CI 0.79 to 2.24 using community controls and 1.04, 95% CI 0.60 to 1.83 using hospital controls).[349] Recent exposure to oral NSAIDs, on the other hand, was associated with increased risk of renal failure using either community (adjusted OR 2.20, 95% CI 1.49 to 3.25) or hospital (adjusted OR 1.84, 95% CI 1.15 to 2.93) controls. We identified no studies comparing the risk of cardiovascular events in persons on topical versus oral NSAIDs.

Topical Salicylates (Including Capsaicin)

We identified no trials comparing topical salicylates to oral or topical NSAIDs. One recent good-quality systematic review found topical salicylates superior to placebo for pain relief when data from six trials were pooled (relative benefit 1.5, 95% CI 1.3 to 1.9; NNT 5.3, 95% CI 3.6 to

10.2).[32] However, the three higher quality trials found no significant benefit (relative benefit 1.3, 95% CI 0.98 to 1.6). Local adverse events were rare, but the quality of adverse-event reporting was poor.

We identified no trials comparing topical capsaicin to oral or topical NSAIDs. One recent good-quality systematic review found that for chronic musculoskeletal pain, capsaicin was superior to placebo for achieving clinical success (defined as approximately a 50% reduction in pain), with a relative benefit of 1.5 (three trials, 95% CI 1.1 to 2.0) and number needed to treat of 8.1 (4.6 to 34).[350] About 54% of patients had local adverse events with capsaicin, compared with 15% with placebo (relative risk 3.6, 95% CI 2.6 to 5.0). Withdrawals due to adverse events were also significantly more likely with capsaicin (13% vs. 3%, relative risk 4.0, 95% CI 2.3 to 6.8). An older systematic review was excluded because it appears outdated.[351]

Chapter 4. Summary and Discussion

The table below summarizes the strength of evidence and results for each key question. Publication bias is an issue for all of these questions, because we do not know the complete details or results of unpublished trials submitted to the FDA or trials that have been conducted but not published or submitted to the FDA

Table 34. Summary of findings with strength of evidence

Key Question	Level of Evidence	Conclusion
1a. What are the comparative benefits and harms of treating osteoarthritis with oral medications or supplements?		
Efficacy: Non-selective NSAID vs. non-selective NSAID	Non-selective NSAID vs. non-selective NSAID: *good.* Consistent evidence from several good-quality systematic reviews and published trials. Salsalate vs. aspirin. *Poor.* One short-term trial. Salsalate or aspirin vs. non-aspirin NSAIDs. *Poor.*	No difference in efficacy between various non-aspirin, non-selective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac). No difference between salsalate and aspirin in one short-term trial. There were no trials or eligible observational studies of salsalate or aspirin vs. non-aspirin NSAIDs.
Efficacy: COX-2 selective vs. non-selective NSAID	Good. Consistent evidence from many published trials	No difference.
Efficacy: COX-2 selective vs. COX-2 selective	Good. Consistent evidence from six published trials.	No clinically significant differences at comparable doses.
GI and CV safety: Rofecoxib	Good. One large published trial, multiple meta-analyses and systematic reviews of published and unpublished trials, multiple observational studies.	In a pivotal, long-term trial (VIGOR) of patients with rheumatoid arthritis, rofecoxib 50 mg daily reduced symptomatic ulcers and serious ulcer complications compared with naproxen. After an average of 9 months, rofecoxib use was associated with 1 fewer symptomatic ulcer for every 62 patients treated; one fewer serious GI complication for every 191; and one additional MI for every 333 patients. The overall rate of serious adverse events, however, was higher with rofecoxib than naproxen. Higher-quality systematic reviews and observational studies are generally consistent with these findings (about 3.5 additional myocardial infarctions for every 1000 patients treated for one year). One long-term placebo-controlled polyp prevention trial also found an increased risk of MI.
GI and CV safety: Celecoxib	Fair: Multiple meta-analyses and systematic reviews of mostly short-term published and unpublished trials, multiple observational studies.	In the only published large, long-term study (CLASS), celecoxib was no better than diclofenac or ibuprofen for complicated or symptomatic ulcers at the end of follow-up. In subgroup analyses of patients not on aspirin, celecoxib was superior to ibuprofen but not to diclofenac for ulcer complications. There was no increase in the rate of cardiovascular events for celecoxib in CLASS. The overall rate of serious adverse events was similar

Key Question	Level of Evidence	Conclusion
		with celecoxib compared to ibuprofen and diclofenac. Systematic reviews and other meta-analyses of primarily short-term, unpublished data and lower doses found celecoxib superior to non-selective NSAIDs for ulcer complications. Observational studies are generally consistent with the short-term trials. However, recent meta-analyses found an increased risk of myocardial infarction with celecoxib compared with placebo (about 3.5 myocardial infarction for every 1000 patients treated for one year), with much of the evidence for increased risk coming from two large polyp prevention trials.
GI and CV safety: Valdecoxib	Fair: Fair quality meta-analyses of published and unpublished trials	Compared to non-selective NSAIDs, valdecoxib was associated with one fewer upper GI complication with valdecoxib for every 78 patients treated for 3 to 6 months. There was no association between valdecoxib and myocardial infarction in primarily short-term chronic pain trials. However, two short-term trials in a high-risk post-coronary artery surgery setting found that valdecoxib was associated with an acute two- to three-fold higher risk of cardiovascular events compared with placebo.
GI and CV safety: Etoricoxib	Fair: Several fair quality meta-analyses of published and unpublished trials	GI safety: Etoricoxib was associated with fewer perforations, symptomatic ulcers, and bleeds than diclofenac, ibuprofen, and naproxen (rate/100 patient-years 1.00 vs. 2.47). CV safety: Based on limited data from short-term trials, etoricoxib has a cardiovascular safety profile similar to non-selective NSAIDs, with the possible exception of naproxen.
GI and CV safety: Lumiracoxib	Fair: One large, long-term trial	GI safety: In patients not taking low-dose aspirin, lumiracoxib was associated with a lower risk of ulcer complications compared to naproxen and ibuprofen (1-year incidence 0.25% vs. 1.09%, p<0.0001). CV safety: There were no differences in the risk of serious CV events (rates ranged from 0.11% to 0.38% after 1 year).
GI and CV safety: Partially selective NSAIDs	GI safety: Fair for meloxicam (short-term RCTs, meta-analyses, observational studies); poor for nabumetone and etodolac CV safety: Poor for all; two observational studies for meloxicam	GI safety: Meloxicam and non-selective NSAIDs were generally associated with similar risks of serious GI events; evidence was insufficient to make reliable judgments about GI safety of nabumetone and etodolac CV safety: Very sparse evidence that meloxicam and non-selective NSAIDs were associated with similar risks of serious CV events; no evidence for nabumetone and etodolac
GI and CV safety: Non-selective NSAIDs	Good for GI safety. Consistent evidence from many published trials, systematic reviews, and observational studies	No clear difference in GI safety between non-selective NSAIDs at commonly used doses. Naproxen was associated with a modest cardiovascular protective effect compared to other NSAIDs in a good-quality systematic

Key Question	Level of Evidence	Conclusion
	Fair for CV safety. No large, long-term controlled trials. Almost all evidence from observational studies	review of observational studies, but methodological issues could have affected the results. Comparative CV safety of other non-aspirin NSAIDs is not clear. A large systematic review of RCTs addressing this issue has not yet been published.
GI and CV safety: Aspirin	Fair. Many trials and systematic reviews, but almost exclusively in patients receiving aspirin at doses used for cardiovascular prophylaxis.	Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds when given in prophylactic doses. There is insufficient evidence to assess safety of aspirin in doses used for pain control compared with non-aspirin NSAIDs.
GI and CV safety: Salsalate	Poor. Flawed observational data	Salsalate was associated with a lower risk of adverse events using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs. Almost no data is available on CV safety.
Mortality	Fair. Individual trials not large enough to detect differences in mortality. One meta-analysis of celecoxib using unpublished information, and one fair-quality observational study of non-selective NSAIDs.	No difference between celecoxib and non-selective NSAIDs, but few deaths occurred. In one cohort study, nabumetone was associated with lower all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
HTN, CHF, edema, and impaired renal function	Fair. Multiple systematic reviews, clinical trials, and observational studies, but analyses limited by inconsistent reporting of results and probable publication bias	All NSAIDs are associated with deleterious effects on blood pressure, edema, and renal function. Indirect evidence and observational data suggests that rofecoxib is associated with a greater risk of hypertension, CHF, and edema compared to celecoxib. Rofecoxib was also associated with more cardiorenal events than celecoxib in three head-to-head trials of high-risk patients, but possible nonequivalent dosing limits interpretation of these results. No clear differences between celecoxib, partially selective, and non-selective NSAIDs.
Hepatotoxicity	Good. Systematic reviews of multiple trials and observational studies	Clinically significant hepatotoxicity was rare. Several NSAIDs associated with high rates of hepatotoxicity have been removed from the market. Among currently marketed NSAIDs, diclofenac was associated with a higher rate of liver-related discontinuations compared with placebo (2.17%).
Tolerability	Good for coxibs and non-selective NSAIDs (consistent results from multiple systematic reviews); fair for partially selective NSAIDs, aspirin, and salsalate (few meta-analyses and short-term trials)	Relative to non-selective NSAIDs, coxibs and partially selective NSAIDs were at least as well tolerated and aspirin was less tolerated; salsalate was less well tolerated than non-selective NSAIDs in 2 of 3 trials, but less toxic in flawed observational studies; no clear differences among coxibs or among non-selective NSAIDs
Acetaminophen	Good overall. Consistent results from multiple systematic reviews for efficacy and GI adverse events. Poor for cardiovascular safety	Acetaminophen is modestly inferior to NSAIDs for reducing pain and improving function. Acetaminophen is superior to NSAIDs for GI side effects (clinical trials data) and GI complications (observational studies).

Key Question	Level of Evidence	Conclusion
	(no evidence on myocardial infarctions) and fair for renal safety (observational studies)	Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies). Acetaminophen does not appear to be associated with an increased risk of hepatotoxicity at therapeutic doses in patients without underlying liver disease.
Glucosamine and chondroitin	Fair. Inconsistent evidence from clinical trials. The most promising results have been obtained in trials funded by a European manufacturer of pharmaceutical grade glucosamine not approved in the U.S.	A recent large, good-quality NIH-funded trial found that pharmaceutical grade glucosamine hydrochloride and chondroitin sulfate alone or in combination were not superior to placebo among all patients studied. In a small subgroup of patients with at least moderate baseline pain, there appeared to be a modest benefit for pain relief from the combination, but this did not appear to be a preplanned analysis. In older trials, many with some flaws, glucosamine was superior to oral NSAIDs and placebo in trials evaluating pharmaceutical grade glucosamine and funded by its manufacturer. Other trials found no difference between glucosamine and placebo or glucosamine and oral NSAIDs. Chondroitin was superior to placebo in older, flawed trials. Data on the effects of glucosamine on slowing progression of disease are limited to two trials showing beneficial effects on progression of knee joint narrowing. Glucosamine and chondroitin were consistently well tolerated, with no serious adverse events reported in the trials.
1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?	Good for safety (consistent evidence from multiple clinical trials and observational studies), no evidence for alternative dosage strategies.	Risk of GI bleeding increases with higher doses of non-selective NSAIDs. Effects of dose and duration are somewhat inconsistent. Celecoxib was most effective for GI safety at 6 months and not after longer follow-up in the CLASS trials. A trend towards a dose-dependent CV risk of celecoxib was observed in a long-term prevention trial. CV risk of rofecoxib became most apparent after 8 months in VIGOR and after 18 months in the APPROVe prevention trial, but interpretation of earlier risk is imprecise because of small numbers of events. Most, but not all, observational studies suggest a dose-dependent effect of rofecoxib on MI risk.
2. Do the comparative benefits and harms of oral treatments for osteoarthritis vary for certain demographic and clinical subgroups?		
Demographic subgroups including age, sex, and race	Good (age, sex) Poor (race)	Most studies included a majority of women. The risks of GI and CV events increase in older patients. The data that selective COX-2 inhibitors are safe and efficacious in different racial groups have been presented to the FDA. In the peer-reviewed literature, there is no evidence that the comparative efficacy of different selective and non-selective NSAIDs varies according to age, gender, or race.

Key Question	Level of Evidence	Conclusion
Pre-existing disease including history of previous bleeding due to NSAIDs or peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure	Previous bleeding: Good Hypertension, edema: Fair Ischemic Heart Disease: Poor (no comparative studies) Heart failure: Fair	Risk of bleeding is higher in patients with prior bleeding or PUD. Two trials found high rates of recurrent ulcer bleeding in patients randomized either to celecoxib or a non-selective NSAID + PPI. Risk of CV and renal events is higher in patients with cardiac and renal co-morbidities. In a single observational study that examined mortality, rofecoxib and non-selective NSAIDs were associated with higher rates of death and recurrent heart failure than celecoxib.
Concomitant anticoagulant use	Fair overall: Primarily observational studies	Concomitant use of anticoagulants and non-selective NSAIDs increase the risk of GI bleeding three- to six-fold. Reliable conclusions about the safety of selective NSAIDs in the setting of anticoagulation could not be drawn from flawed observational studies, though there are case reports of serious bleeding events (primarily in the elderly). Warfarin plus aspirin (prophylactic doses) increased the risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis. Acetaminophen can increase INR levels, but effects on bleeding rates have not been studied.
Concomitant aspirin use	Good for GI safety: Consistent evidence from clinical trials and observational studies Fair for CV safety: Subgroup analyses from few trials, few observational studies	Concomitant use of aspirin appears to attenuate or eliminate the GI benefits of selective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in patients on celecoxib and those on non-selective NSAIDs in one meta-analysis. In one trial, rofecoxib plus low-dose aspirin and ibuprofen were associated with a similar risk of endoscopic ulcers (16-17%); both were significantly higher than placebo (6%) or aspirin alone (7%). Evidence regarding the effects of concomitant aspirin use on CV risk associated with selective or non-selective NSAIDs is limited, though three polyp prevention trials of rofecoxib or celecoxib found that concomitant aspirin use did not attenuate the observed increased risk of CV events.
3. What are the comparative effects of co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs) on the gastrointestinal harms associated with NSAID use?	Good: Consistent evidence from good-quality systematic reviews and numerous clinical trials	Co-prescribing of misoprostol or PPIs with NSAIDs offers some advantages over full-dose H2-antagonists. PPIs are associated with the lowest rates of endoscopically detected *duodenal* ulcers. Misoprostol and PPIs are associated with similar rates of endoscopically detected *gastric* ulcers as PPIs. While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of clinical GI events, it is also associated with an increased risk of GI-related adverse event withdrawals. Full-dose H2 blockers were associated with lower ulcer risk than placebo, but head-to-head trials against PPIs and misoprostol are lacking. Endoscopic duodenal ulcer risk for *standard* dose H2

Key Question	Level of Evidence	Conclusion
		blockers was lower than placebo, similar to misoprostol, and higher than omeprazole; *standard* dosages of H2 blockers and placebo were associated with similar gastric ulcer risk
4. What are the comparative benefits and harms of treating osteoarthritis with oral medications as compared with topical preparations?		
Topical NSAIDs: efficacy	Good: Consistent evidence for selected topical NSAIDs from clinical trials	Topical NSAIDs are similar to oral NSAIDs for efficacy. Topical diclofenac is the best studied, though many trials evaluated a formulation using a DMSO carrier that is not available in the U.S. Topical ibuprofen was superior to placebo in several trials.
Topical NSAIDs: safety	Good: Consistent evidence from trials and systematic reviews and observational studies	Topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. Total adverse events and withdrawal due to adverse events are similar. Topical NSAIDs are superior for GI events, including severe events, and changes in hemoglobin (data from one good-quality trial).
Topical salicylates: (including capsaicin)	Fair: Only placebo-controlled trials, many of which were flawed	Topical salicylates were no better than placebo in higher-quality trials. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events.

Discussion

This report provides a comprehensive summary of the comparative efficacy and safety of oral nonsteroidal anti-inflammatory drugs (NSAIDs) (selective, non-selective, aspirin, and salsalate), acetaminophen, certain over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) that are commonly used for pain control and improvement of functional status in patients with osteoarthritis. At this time, no drug or supplement is known to modify the course of disease, though initial long-term trials of pharmaceutical grade glucosamine suggest an effect on radiologic evidence for disease progression.

Evidence regarding the benefits of oral NSAIDs from primarily short-term randomized controlled trials is abundant and demonstrates no clear, consistent differences for relieving pain or other osteoarthritis-related symptoms, or for superior tolerability. On the other hand, much of the uncertainty and confusion regarding NSAIDs centers on their comparative safety.

The trade-offs between reduced GI risk and increased CV harms was first clearly observed in VIGOR. In this trial, rofecoxib 50 mg daily significantly reduced symptomatic ulcers (NNT=62) and serious ulcer complications (NNT=191) compared with naproxen in patients with rheumatoid arthritis.[19] However, the GI-protective effects were accompanied by a more than four-fold increase in myocardial infarctions, or one additional myocardial infarction for every 333 patients treated with rofecoxib. When considering all "serious" adverse events, moreover,

rofecoxib was not associated with any clear benefit compared with naproxen.[114]

Rofecoxib became the focus of intense scrutiny following publication of VIGOR. Subsequently, multiple observational studies[138-141, 143-152] and systematic reviews[124, 129] of RCTs have reported findings largely consistent with an increased risk of cardiovascular events with exposure to rofecoxib. Rofecoxib was voluntarily withdrawn from the market in 2004, after a long-term placebo-controlled polyp prevention trial reported increased cardiovascular risk.[132] Valdecoxib was likewise voluntarily withdrawn from the market in 2005. Withdrawal was recommended by FDA based on their conclusion that valdecoxib associated with no clear GI benefit,[117] an increased risk of serious skin reactions,[168] and potential increased risk of CV events.[165, 166] As a result, celecoxib is the only selective NSAID currently available in the U.S.

The same concerns about the overall safety of rofecoxib have been directed at celecoxib. The evidence regarding the relative GI and CV safety of celecoxib, however, is less clear. In CLASS, the largest published study of GI complications, celecoxib was not significantly different than diclofenac or ibuprofen for either ulcer complications or myocardial infarctions by the end of follow-up.[94] Like the VIGOR trial, re-analysis of all serious adverse events in CLASS found no significant advantage for celecoxib.[94] On the other hand, systematic reviews and other meta-analyses of primarily short-term and frequently unpublished data found that celecoxib (primarily at lower doses than were used in CLASS) was associated with lower rates of ulcer complications than non-selective NSAIDs.[62, 121] These findings, in combination with earlier systematic reviews of primarily short-term trials that found no increased cardiovascular risk with celecoxib, suggested a possible advantage of celecoxib over non-selective NSAIDs.[62, 134, 135] More recent meta-analyses (including data from long-term polyp prevention trials) reporting an increased risk of myocardial infarctions with celecoxib (particularly at high doses) relative to placebo, however, raise additional questions about its appropriate use.[129, 136]

Well-designed, long-term observational studies could provide 'real-world' information not available from most RCTs, which are usually designed as short-term efficacy trials that evaluate selected populations and employ rigid dosing regimens (often at high doses) under carefully controlled conditions. Observational studies are generally consistent with the RCTs in that celecoxib is consistently GI protective[139, 162] or neutral[138] and not associated with higher risks of CV events relative to non-selective NSAIDs.[144, 145, 150, 160] Additionally, celecoxib is associated with lower risks of serious GI events than rofecoxib.[139, 142] Evidence from observational studies is less clear with regard to how celecoxib compares to rofecoxib in terms of CV risk due to differences in outcome reporting and in the number and type of factors adjusted for in outcome analyses.

An important drawback of the observational studies, however, is that they largely focus on individual adverse events in isolation. More informative analyses of the overall trade-off between risks and benefits would consider net harms from all serious adverse events. Our re-analysis of results from three studies[139, 147, 163] reporting myocardial infarctions, heart failure hospitalizations, and gastrointestinal bleeding in an elderly Canadian population receiving multiple prescriptions suggests that in everyday use, celecoxib may confer net advantages in terms of the number of these events compared with rofecoxib and non-selective NSAIDs. However, additional studies on original data are needed to confirm this finding in other settings.

The cardiovascular effects of naproxen and other non-selective NSAIDs have been the subject of considerable debate since the publication of the VIGOR trial. At this time, among NSAIDs with sufficient evidence to assess cardiovascular risk, naproxen appears to offer the most favorable cardiovascular safety profile. In a recent, comprehensive systematic review,

naproxen (even at high doses) was moderately superior to COX-2 inhibitors for cardiovascular safety.[129] In addition, naproxen was the only NSAID (selective or non-selective) associated with a neutral cardiovascular effect relative to placebo, though these analyses were primarily based on indirect comparisons. The cardiovascular risks of non-naproxen, non-selective NSAIDs were similar to the selective COX-2 inhibitors, though most of the evidence was limited to high-dose ibuprofen and diclofenac. At this time, there is insufficient evidence to reliably judge the relative cardiovascular safety of other non-selective NSAIDs or the partially selective drugs nabumetone, diclofenac, and meloxicam. For GI safety, no clear advantage for any particular partially selective or non-selective NSAIDs has been demonstrated.

Topical NSAIDs may offer the advantages of local analgesic and anti-inflammatory effects without the systemic side effects of oral administration. They would probably be most useful in patients with a limited number of affected joints. Although topical NSAIDs appear comparable to oral NSAIDs for pain relief in several trials, the most convincing evidence comes from a recent trial that evaluated a proprietary formulation of diclofenac with DMSO that has not been FDA-approved.[338] Topical NSAIDs appear safer than oral NSAIDs for GI safety, but data on comparative cardiovascular risks are not available. The relative benefits of topical rubefacients compared with topical or oral NSAIDs has not been adequately studied, and other than for capsaicin (which is sometimes classified separately from the rubefacients), there is insufficient evidence to prove that topical rubefacients are superior to placebo for osteoarthritis.

Acetaminophen is often considered an attractive alternative to NSAIDs because of its perceived safety profile. It was associated with GI-protective effects relative to non-selective NSAIDs,[229, 231] though at the expense of modestly inferior efficacy.[234] More evidence is needed to compare the effects of acetaminophen and NSAIDs on other important adverse events such as cardiovascular safety, renal dysfunction, blood pressure, and heart failure. However, one recent observational study found that heavy use of acetaminophen is associated with increased cardiovascular risks similar to that seen with NSAIDs.[237] Aspirin is another alternative that has the advantage of a cardiovascular protective effect. However, nearly all of the evidence on cardiovascular and GI safety of aspirin is from trials using lower, preventative doses rather than higher anti-inflammatory and analgesic doses.

Glucosamine and chondroitin are widely available as over-the-counter supplements. The highly variable content of currently available products, however, remains a significant issue in the U.S. Further, nearly all of the trials demonstrating benefits of glucosamine have been conducted using pharmaceutical grade preparations not currently available in the U.S.[248] Compared with the evidence for glucosamine, the evidence for chondroitin appears less promising. While these agents appear to be safe in the short term, high-quality, long-term safety data are sparse. A recent large, NIH-sponsored trial helps clarify the role of these supplements in management of osteoarthritis.[259] It found that the combination of pharmaceutical grade glucosamine and chondroitin was modestly superior to placebo only in an analysis of a small subgroup of patients with at least moderate severity of baseline disease. Neither glucosamine nor chondroitin alone was superior to placebo overall or in the subgroup of patients with greater baseline severity. Data on effects of glucosamine on osteoarthritis progression are limited to two trials showing a beneficial effect on knee joint space narrowing over three years using a pharmaceutical grade preparation.

Strategies to reduce the risk of GI complications in patients taking NSAIDs include co-prescription of misoprostol, standard- or double-dose H2 blockers, or PPIs. All of these strategies are effective in reducing the risk of NSAID-associated *endoscopic* gastric and

duodenal ulcers relative to use of non-selective NSAIDs alone. Misoprostol (RR 0.36, 95% CI 0.20 to 0.67) and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers.[293] Further, misoprostol is the only agent proven to decrease risk of clinical GI events, but is associated with an increased risk of withdrawals due to nausea, diarrhea, and/or abdominal pain.[317] In high-risk patients (those with a recent bleed), non-selective NSAIDs and the combination of a non-selective NSAID plus a PPI were both associated with similar, high rates of recurrent bleeding.[270, 271]

In summary, each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. The role of selective and non-selective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence varies, no currently available analgesic reviewed in this report offers a clear overall advantage compared with the others, which is not surprising given the complex trade-offs between the many benefits (pain relief, improved function, improved tolerability, and others) and harms (cardiovascular, renal, GI, and others) involved. In addition, individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of a small increase in CV risk, for example, could be an acceptable trade-off for many patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and cardiovascular events), co-morbid conditions, and concomitant medication use (such as aspirin and anticoagulation). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant trade-offs.

Chapter 5. Future Research

- Nearly all of the clinical trials reviewed in this report were "efficacy" trials conducted in ideal settings and selected populations. "Pragmatic" trials that allow flexible dosing or medication switches and other clinical trials of effectiveness would be very valuable for learning the outcomes of different analgesic interventions in real-world settings.

- The cardiovascular safety of non-selective NSAIDs has not been adequately assessed in large, long-term clinical trials. Naproxen in particular may have a different cardiovascular safety profile than other NSAIDs and should be investigated in long-term, appropriately powered trials. The cardiovascular risks associated with the partially selective NSAIDs meloxicam, nabumetone, and diclofenac also have not been well studied.

- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms, but have generally had a narrow focus on single adverse events. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall trade-offs between benefits and harms.

- The cardiovascular risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.

- Meta-analyses of the risks associated with selective COX-2 inhibitors need to better assess for the effects of dose and duration, as most of the cardiovascular risks have only occurred with prolonged use and at higher doses.

- Large, long-term trials of the GI and cardiovascular safety associated with full-dose aspirin, salsalate, or acetaminophen compared with non-aspirin NSAIDs or placebo are lacking.

- Given the large number of patients who meet criteria for aspirin prophylaxis for cardiovascular events, more trials evaluating the effects of low-dose aspirin on GI and CV risks are needed.

- Trials and observational studies evaluating comparative safety or efficacy should be sufficiently inclusive to evaluate whether effects differ by race or gender.

- Genetic testing could theoretically help predict patients who are at higher risk of cardiovascular complications from selective COX-2 inhibitors because of differences in the COX-2 gene promoter or other genes. This is a promising area of future research.

- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies. In addition, although there is speculation that once daily versus twice daily dosing of certain COX-2 inhibitors could affect CV risk, this hypothesis has not yet been tested in a clinical trial.

- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical grade glucosamine not available in the U.S. and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations to oral NSAIDs are needed, as these are likely to remain available even if the FDA approves a pharmaceutical grade glucosamine. Additional long-term trials are also required to further evaluate effects of glucosamine on progression of joint space narrowing.

- No topical NSAIDs are FDA-approved in the U.S., yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO. A UK trial of topical versus oral ibuprofen is currently in progress and will help clarify the benefits and safety of topical versus oral NSAIDs. However, cohort studies using large observational databases may be required to adequately assess cardiovascular risk.

Addendum

As this report was going to press, two relevant meta-analyses on risks associated with NSAIDs were published. We were unable to fully incorporate these studies into our report, but their results generally appear consistent with our conclusions.

One meta-analysis evaluated risk of renal events (peripheral edema, hypertension, or renal dysfunction) and arrhythmias from 114 randomized trials of COX-2 selective NSAIDs [Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events. Meta-analysis of randomized trials. *JAMA*. 2006;296:(doi:10.1001/jama.296.13.jrv6001)]. It was rated fair-quality because it did not assess the quality of included studies. It found rofecoxib associated with increased risks of arrhythmia relative to control (placebo, other NSAID, or mixed/other) treatments (RR 2.90, 95% CI 1.07 to 7.88), though the number and rate of events was low (13/10126 or 0.1% in the rofecoxib arms, with 10 of the events ventricular fibrillation, cardiac arrest, or sudden cardiac death). The increase in risk was equivalent to about 1.1 additional arrhythmia events per 1000 patients treated with rofecoxib. Rofecoxib was also associated with an increased risk of peripheral edema (RR 1.43, 95% CI 1.23 to 1.66), hypertension (RR 1.55, 95% CI 1.29 to 1.85) and renal dysfunction (RR 2.31, 95% CI 1.05 to 5.07). For composite renal events (peripheral edema, hypertension, or renal dysfunction), risks were significantly higher with increased dose and increased duration of rofecoxib. Celecoxib was associated with lower risks of renal dysfunction (RR 0.61, 95% CI 0.40 to 0.94) and hypertension (RR 0.83, 95% CI 0.71 to 0.97) than control treatments, though there was no difference for composite renal events (RR 0.97, 95% CI 0.84 to 1.12) or arrhythmia (RR 0.84, 95% CI 0.45 to 1.57). There was no clear association between other COX-2 inhibitors (valdecoxib/parecoxib, etoricoxib, or lumiracoxib) and arrhythmia or renal events, though there was a trend towards increased renal events with valdecoxib/parecoxib (RR 1.24, 95% CI 1.00 to 1.55), and no arrhythmia events were reported in six trials of lumiracoxib.

Several factors complicate interpretation of estimates of arrhythmia risk from this meta-analysis. First, the rate of arrhythmias varied widely between control arms for different COX-2 selective inhibitors. For example, the rate of arrhythmias was fourteen-fold higher in the control arms of the celecoxib trials compared to the control arms of the rofecoxib trials (18/6568 or 0.3% vs. 2/10,126 or 0.01%). In addition, the proportion of specific arrhythmia events varied widely between drugs. For valdecoxib, over half (69/129 or 53%) of the arrhythmia events were atrial fibrillation, compared to 14% (3/22) for celecoxib and 8% (1/13) for rofecoxib. Finally, even though funnel plots and statistical tests did not suggest the presence of publication bias, only a minority of trials reported usable data on arrhythmia events. For example, only 10 of 37 included trials of celecoxib (accounting for about one-third of trial participants) had data that could be used in the analysis of arrhythmia events.

The second meta-analysis evaluated cardiovascular risk (primarily myocardial infarction) associated with NSAIDs from 23 observational studies (mostly of older populations) [McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase. A systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;296:(doi:10.1001/jama.292.13.jrv60011)]. Its results are largely consistent with our

qualitative assessment of cardiovascular risk from the observational literature. This meta-analysis appears to meet criteria for a good-quality systematic review, but its interpretation is complicated by the presence of substantial ($p<=0.001$), unexplained between-study heterogeneity for the main pooled analyses. It found rofecoxib associated with an increased risk of cardiovascular events at both lower (25 mg/day or less, RR 1.33, 95% CI 1.00 to 1.79) and higher (>25 mg/day, RR 2.19, 95% CI 1.64 to 2.91) doses, with the increased risk observable during the first month of treatment. Of the other NSAIDs, diclofenac (RR 1.40, 95% CI 1.16 to 1.70) was associated with the greatest cardiovascular risk, followed by indomethacin (RR 1.30, 95% CI 1.07 to 1.60) and meloxicam (RR 1.25, 95% CI 1.00 to 1.55). Celecoxib (RR 1.06, 95% CI 0.91 to 1.23), naproxen (RR 0.97, 95% CI 0.87 to 1.07), piroxicam (RR 1.06, 95% CI 0.70 to 1.59), and ibuprofen (RR 1.07, 95% CI 0.97 to 1.18) were not associated with increased risks. Only 3 of the 23 included studies reported adjusting for over-the-counter aspirin or NSAID use; two other studies included patients shortly after myocardial infarction that were all prescribed or presumed to be on aspirin.

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